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Research article

Spontaneous sensorimotor cortical activity is suppressed by deep brain stimulation in patients with advanced Parkinson's disease

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ABSTRACT

Advanced Parkinson's disease (PD) is characterized by an excessive oscillatory beta band activity in the subthalamic nucleus (STN). Deep brain stimulation (DBS) of STN alleviates motor symptoms in PD and suppresses the STN beta band activity. The effect of DBS on cortical sensorimotor activity is more ambiguous; both increases and decreases of beta band activity have been reported. Non-invasive studies with simultaneous DBS are problematic due to DBS-induced artifacts. We recorded magnetoencephalography (MEG) from 16 advanced PD patients with and without STN DBS during rest and wrist extension. The strong magnetic artifacts related to stimulation were removed by temporal signal space separation. MEG oscillatory activity at 5–25 Hz was suppressed during DBS in a widespread frontoparietal region, including the sensorimotor cortex identified by the cortico-muscular coherence. The strength of suppression did not correlate with clinical improvement. Our results indicate that alpha and beta band oscillations are suppressed at the frontoparietal cortex by STN DBS in PD.

1. Introduction

Parkinson's disease (PD) is a progressive extrapyramidal movement disorder. Abnormal oscillatory activity occurs within the basal ganglia in PD. This abnormal activity is modified by the stimulation of different cerebello–thalamo–cortical structures, restoring normal unsynchronized activity in the basal ganglia circuitry and reducing the clinical symptoms of PD [1]. One important hub of this network is the subthalamic nucleus (STN). Deep brain stimulation (DBS) of the STN effectively alleviates PD symptoms [2,3] although the physiological basis of DBS efficacy remains poorly understood.

Direct local field potential recordings (LFPs) from STN indicate a pathological role for oscillations at about 10–30 Hz. STN DBS suppresses this oscillatory activity during or after periods of stimulation. Moreover, lower oscillatory activity after STN DBS is associated with better motor task performance (for references, see [4]). STN oscillatory signals may be a useful marker in a brain-computer interface controlling DBS [5].

In rat models of PD, the optical stimulation of primary motor cortex ameliorates PD symptoms [6], and abnormal cortical beta band oscillations are suppressed by STN stimulation in parallel with improved movements [7]. In humans, STN activity is coherent with EEG recorded over the sensorimotor areas [8]. In three patients, beta band electro-corticographic (ECoG) activity was suppressed during DBS in the motor cortex close to the cortical end of the hyperdirect pathway connecting STN and cortex [9]. An 11% decrease of EEG alpha band peak amplitude around 9–10 Hz occurs during DBS mainly in the frontocentral regions [10].

Magnetoencephalography (MEG) is an excellent tool for non-invasive studies for cortical electrophysiology. Severe electromagnetic artifacts generated by the stimulator complicate MEG studies on patients with DBS. An artifact suppression algorithm, however, enables the analysis of MEG also during DBS stimulation [11–14]. Both decreases [15,16] and increases [14] of sensorimotor beta band MEG activity have been reported with DBS delivered during rest. Simultaneous recordings from STN and MEG suggest that DBS suppresses the synchronization of beta band activity between the STN and supplementary motor areas [17]. For a recent review of the MEG studies of DBS, see [18].

Cortico-muscular coherence (CMC) is another measure of beta-band

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cortical activity, reflecting connectivity between the sensorimotor cortex and contracted muscles [19]. DBS has a varying effect on CMC in patients with PD [20].

Here we further clarify the DBS modifications of cortical spontaneous MEG and CMC at the sensor level when brain activity was recorded during DBS on and off conditions. We studied the effects of DBS in both rest and active conditions.

2. Material and methods

2.1. Patients

Eighteen patients with advanced PD and bilateral STN DBS were studied. Data of two patients was excluded: one had only a minimal amount of acceptable data during the motor task (see below), and another did not have a clear CMC peak. In the remaining sixteen patients (mean age 57 ± 11 years; 11 male, 5 female) four had a Medtronic Kinetra and twelve a Medtronic Activa PC stimulator. The patients had no clinical signs of dementia, psychosis, or depression. The active contacts, voltage, pulse width, and frequency of the stimulator were individually optimized for optimal therapeutic efficiency. The measurements were made 2–24 months after the DBS implantation. All patients used their normal antiparkinsonian medication during MEG measurements. Table 1 describes clinical details of the patients and DBS settings. The study was approved by the Ethics Committee of Helsinki University Hospital and all patients gave an informed written consent. Data from four patients were reported previously in [15] and motor task related data from 13 patients in [20].

2.2. Data acquisition and experimental paradigm

The MEG signals were recorded with a 306-channel Elekta Neuromag MEG device (Elekta Oy, Helsinki, Finland) inside a magnetically shielded room (Euroshield, Eura, Finland). The sampling frequency was 1012 Hz and the recording passband 0.03–330 Hz. A nurse monitored the patient inside the shielded room. The patient's head with respect to the MEG sensors was localized by activating the head position indicator (HPI) coils at the beginning of the measurements in patients 1–13 and continuously for patients 14–16.

MEG was recorded for three minutes with eyes closed and for five minutes with eyes open. Thereafter, patients extended the wrist of the more strongly affected upper limb five times for one minute, with a 20-s rest periods between the extensions. Simultaneously, muscle activity was recorded with surface EMG from extensor carpi radialis longus muscle. The MEG was measured twice, first with DBS on and then with DBS off. The DBS switching was done in the shielded room. The patient, seated on the measurement chair, was taken out from the sensor helmet to get some distance between the MEG sensors and the programmer device. Shifting the patient from under the MEG device, turning the stimulator off, repositioning the patient and relocalization of the head position took approximately 10 min. The patient's Unified Parkinson's Disease Rating Scale (UPDRS-III motor) scores were measured before (DBS on) and after the MEG measurement (DBS off). For one patient, the UPDRS scores were not available.

The amount of successfully collected data during the wrist extension varied particularly when DBS was off as patients were often unable to maintain the extension for one minute. Moreover, EMG signal was unstable at the beginning of each extension. We selected stable intervals for the motor task analysis by manually inspecting the variance of the EMG signal. We matched the data set length between the two measurements by excluding data if necessary to avoid any bias in coherence. On average, 268 ± 14 s of spontaneous MEG and 223 ± 32 s of MEG during the wrist extension were analyzed.

2.3. Data preprocessing

DBS produced large artifacts in the MEG signals. Prominent high-frequency stimulation artifacts were seen at the DBS frequency and its harmonics, particularly in monopolar recordings [13]. In addition, subject movement induced low-frequency artifacts from the pulse generator and the implanted wires on the neck. These artifacts may be as large as several nanoteslas, i.e. approximately 1000 times as large as the largest signals created by spontaneous brain activity. However, the spatiotemporal signal space separation method (tSSS [21];), suppressed these artifacts by projecting out temporal patterns specific to the DBS stimulation artifacts [11–15], resulting in satisfactory data quality. We applied tSSS using Elekta MaxfilterTM software (version 2.2.15). The correlation coefficient was set to 0.8. This value efficiently suppressed artifacts close to the sensors, but did not suppress brain signals [22]. The processing window length was 8 s.

All subsequent analyses were done with FieldTrip (version 2014-03-05 [23],) and MATLAB (www.mathworks.com, version R2008b) unless otherwise noted. After applying Maxfilter™, the data still contained narrow-band DBS interference in the DBS stimulation frequency, its harmonics and aliased harmonics. Additionally, part of the artifacts resided outside these frequencies. Therefore, we identified artifact spikes below 50 Hz from the power spectral density calculated using four-second Hanning windows with 50% overlap, resulting in a frequency resolution of about 0.25 Hz. We filtered out the frequencies containing these artifacts from the MEG data by a fourth-order band-stop Butterworth filter. The same filtering was done for both DBS conditions. In addition, MEG was high-pass filtered from 1 Hz and EMG from 5 Hz.

We divided the filtered data into segments of about one second and applied multitaper spectral analysis [24]. The resulting frequency resolution was approximately 1 Hz. FieldTrip optimizes the number of tapers based on a smoothing window parameter: we used a smoothing window of 6 Hz (± 3 Hz around each frequency). The analyzed frequencies were 5–43 Hz. The analysis was done for gradiometers. The data of each gradiometer pair was combined in power and coherence analysis.

We computed a relative power change, defined as $(P_{DBSon} - P_{DBSoff})/P_{DBSon}$, of the spontaneous MEG data and the data during the wrist extension. In most patients, the relative power was decreased at mid-frontal sensors with DBS on. To analyze this further, we visually identified the frequencies of maximum power decrease for each patient both in spontaneous MEG and during the motor task. They varied between 11–25 Hz. To compare power change between patients, we estimated a single power value over the 11–25 Hz band using a smoothing window of 14 Hz that covered this band. In addition, we calculated the suppression in 5–11 Hz band to study the behavior of the low-frequency component of the sensorimotor mu rhythm. The distribution of the power change in Patient #4 is shown in Fig. 1.

We calculated the CMC between gradiometer pairs and the EMG for both DBS conditions during the motor task. When analyzing coherence at the group level, we applied a normalizing Fisher's z-transformation to the square root of the CMC according to [25]: $\gamma_z = \text{arctanh}(\gamma)$. The EMG signal was not rectified before the CMC calculation as rectification may impair the coherence [26]. We display the CMC maps for qualitative comparison of the extents of CMC and DBS-induced spontaneous activity modifications. In our earlier analysis sharing most of the same patients, the effect of STN DBS on CMC was variable [20].

2.4. Statistical analysis

The group level statistical analysis was done with non-parametric cluster-based statistics [27]. It tests for clusters in the data that pass a specific sample-level statistics, and compares statistics derived from these clusters against statistics obtained from a permutation distribution created by the Monte Carlo method. The permuted units were the

Table 1
Clinical details of patients and DBS parameters.

Patient	Gender	Age	Disease duration before operation (years)	Time since STN stimulator implanted (months)	UPDRS when DBS on	UPDRS when DBS off	LEDD (mg)	DBS voltage right / left (V)	DBS (bipolar or monopolar) right/ left	DBS frequency (Hz)	DBS pulse width right / left (μs)
#1	M	49	9	25	16	25	1555	3.9 / 3.4	bi (3+,2-)/ bi (6+,5-)	130	90 / 90
#2	F	67	11	3	12	14	1115	2.4 / 2.4	mono (2-)/bi (6+,5-)	130	60 / 60
#3	M	59	11	24	17	20	1285	2.5 / 2.3	bi (2+,1-)/bi (6+,5-)	130	60 / 60
#4	F	65	10	2	16	23	1060	2.4 / 2.2	bi (2+,1-)/ bi (6+,5-)	130	60 / 60
#5	M	57	16	6	–	19	1460	2.5 / 2.5	bi (2+,1-) / mono (10-)	130	60 / 60
#6	F	75	10	3	50	50	510	2.3 / 2.2	mono (2-)/ mono (5-)	130	60 / 60
#7	F	66	18	6	10	20	850	2.5 / 3.6	bi (1+,2-)/ mono (10-)	130	60 / 60
#8	M	43	10	6	21	60	670	3.2 / 3.2	mono (1-)/ mono (10-)/	130	60 / 60
#9	M	64	9	6.5	22	38	560	2.3 / 2.3	mono (2)/ mono (10-)	130	60 / 60
#10	M	36	8	6	26	71	210	3.0 / 3.0	mono (2-)/ mono (9-)	130	60 / 60
#11	M	63	18	5	20	21	1550	3.3 / 2.8	mono (1-)/ mono (8-)	130	60 / 60
#12	M	71	8	7	12	27	820	3.7 / 3.7	mono (1-)/ bi (9+, 10-)	130	60 / 60
#13	M	50	14	12	18	24	1000	3.8 / 3.5	bi (2+,3-)/ mono (11-)	150	60 / 60
#14	M	47	8	6	6	45	460	2.3 / 2.5	mono (1-)/ mono (9-)	180	60 / 60
#15	M	42	6	19	6	17	1645	5.9 / 3.6	bi (2+,1-)/ bi (10+,9-)	130	90 / 60
#16	F	64	25	7.5	18	40	650	3.4 / 1.4	bi (2+,1-)/ bi (8+,9-)	160	60 / 60
mean	–	57.4	11.9	9.0	18.0	32.1	962.5	–	–	136.3	–
std	–	11.5	5.0	7.2	10.5	16.8	443.4	–	–	14.5	–

Bi = bipolar, DBS = deep brain stimulation, F = female, LEDD = levodopa equivalent daily dose, M = male, mono = monopolar, STN = subthalamic nucleus, UPDRS = Unified Parkinson's Disease Rating Scale III. Electrodes in the right lead are numbered from 0 to 4; corresponding numbers in the left lead are 8-11. Mean and standard deviations (where appropriate) are shown in the last two rows.

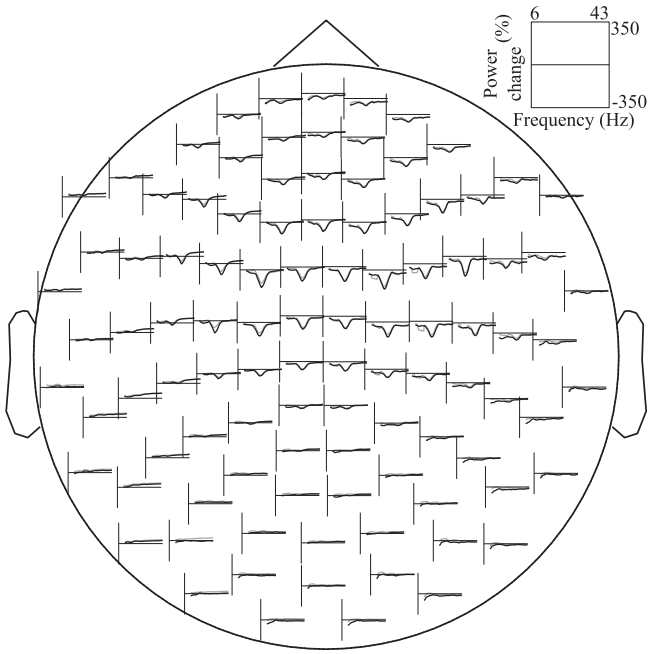

Fig. 1. Relative power change at the sensor level for patient #4. The power decrease peaks at 22 Hz. The gray lines denote the power change during spontaneous activity and the black lines power change during the right wrist extension. Negative: power decrease; positive: power increase when DBS on.

DBS conditions within each subject and the clustered units were the gradiometer pairs. The null hypothesis was that the results from both DBS conditions are derived from the same probability distribution. This non-parametric approach inherently handles the problem of multiple comparisons arising in situations with multiple sensors.

We tested the power change at the sensor level using the 5–11 and 11–25 Hz bands. The side of the wrist extension was not considered in the power analysis of the MEG recorded during the motor task. We used a dependent samples *t*-test for the sample-level statistics and maximum of sums of the T-statistics of all the clusters as cluster-level statistics. A permutation distribution was created with 10 000 randomizations. We used a two-tailed test for both positive and negative power change and report corrected p-values for the two-tailed test. A p-value of less than 0.05 was considered significant. The cluster with the smallest p-value is reported as the p-value from a cluster-based test.

We tested for correlation between power changes during the resting state and the motor task, and corresponding changes in UPDRS III total scores by Spearman's rank correlation. These results were not significant.

3. Results

The spontaneous MEG power at the sensor level in 11–25 Hz band differed significantly between DBS on and DBS off conditions ($p = 0.0052$ for one cluster) when eyes were open. This was the most evident as power decrease over bilateral frontoparietal regions when DBS was on (Fig. 2). The average power change over the cluster of sensors indicated by the statistical test was $-44 \pm 61\%$, with 14 patients out of 16 having a lower power when DBS was on.

In eyes closed and wrist extension conditions, we observed smaller, non-significant suppressions in the same regions ($p = 0.2074$ and $p = 0.2214$, respectively). The average power change in the same cluster as in the spontaneous MEG was -40 ± 67% and $-32 \pm 51\%$ for the eyes closed and wrist extension conditions, respectively, with 12 out of 16 patients having a lower power with DBS on. The average power was 6% stronger in the spontaneous MEG than during the wrist extension when DBS was on; with DBS off the difference was 17%.

In the 5–11 Hz band, a similar power decrease encompassed approximately the same regions (Fig. 2). When eyes were open, the suppression was significant ($p = 0.0108$ for one cluster). Non-significant suppressions occurred also in eyes closed and wrist extension conditions.

The DBS-induced MEG power changes and the corresponding total UPDRS-III score changes were not correlated significantly. Patient 9 who had, contrary to the general trend, higher MEG power when DBS was on had also the largest resting tremor subscores when DBS was off and the largest decrease of tremor subscores when DBS was turned on.

The average CMC had a maximum contralateral to the extended hand overlapping the estimated sensorimotor regions (Supplementary Figure). The field distribution of CMC was more limited than the extent of the suppression of spontaneous 5–25 Hz activity by DBS (Fig. 2).

4. Discussion

We detected a significant power decrease of spontaneous MEG at 5–25 Hz when DBS was on and eyes were open in patients with advanced PD. This power change was the clearest in the sensors displaying the highest CMC during the wrist extension.

4.1. Modifications of brain electrophysiology by DBS

The 10–30 Hz activity was suppressed during DBS in ECoG recordings over the motor cortex in three patients [9]. The measurements were, however, made with 1 x 6 cm electrode strips having a limited spatial sampling. Our data suggest a more widespread effect, in line with the reported distribution of STN-cortex coherence in the beta band [28,29], and suppression of beta-band coherence between the STN and supplementary motor areas during DBS [17]. A similar but non-significant suppression was observed in eyes closed condition. The occipital alpha rhythm dominates spontaneous MEG when eyes are closed and probably dilutes the effect of DBS on spontaneous activity. Suppression of 5–25 Hz activity by DBS was seen also during the tonic muscle contraction but was not significant, possibly because the contraction suppressed the beta band strength [19,30].

Our results indicate that STN DBS suppresses spontaneous cortical oscillatory activity in PD patients. The previous MEG studies of spontaneous activity with simultaneous DBS suggest an average decrease in the alpha and beta band activities [15,16], an increase in the 14–18 Hz range over diffuse cortical areas [14] or no effect [17]. Recently, Abbasi et al. [16] described the effects of unilateral DBS, delivered one day after implantation, on MEG alpha- and beta band activity. Suppressions similar to our observations were seen; the suppressed sources, analyzed with a beamformer, were centered on bilateral sensorimotor cortices, but extended to secondary sensory and premotor areas and supplementary motor cortices. Our results support the similar suppression of alpha and beta band activity also in the chronic DBS therapy.

The modifications of spontaneous brain oscillations in PD may relate to the pathological processes leading to clinical symptoms, or to compensatory mechanisms induced by dopamine depletion [31,32]. The oscillatory synchronization indexed by beta activity in the STN LFP may be at least a faithful biomarker of PD impairment if not causally important [5]. The present results suggest an analogous biomarker role to cortical oscillatory activity depicted by MEG as we did not find correlation between power of spontaneous activity and UPDRS changes.

One patient had an increase in beta band power during DBS. Notably, he also had the most severe resting tremor as displayed in UPDRS subscores when DBS was off; the tremor virtually disappeared during DBS. Parkinsonian tremor suppresses the spontaneous sensorimotor activity [33] and the sensorimotor beta band MEG in PD patients with STN electrodes [31]; as DBS alleviated the tremor, this could explain beta band increase during DBS on in this patient. The three other patients with milder resting tremor had the beta band power decrease by DBS. The possible contribution of tremor to the power

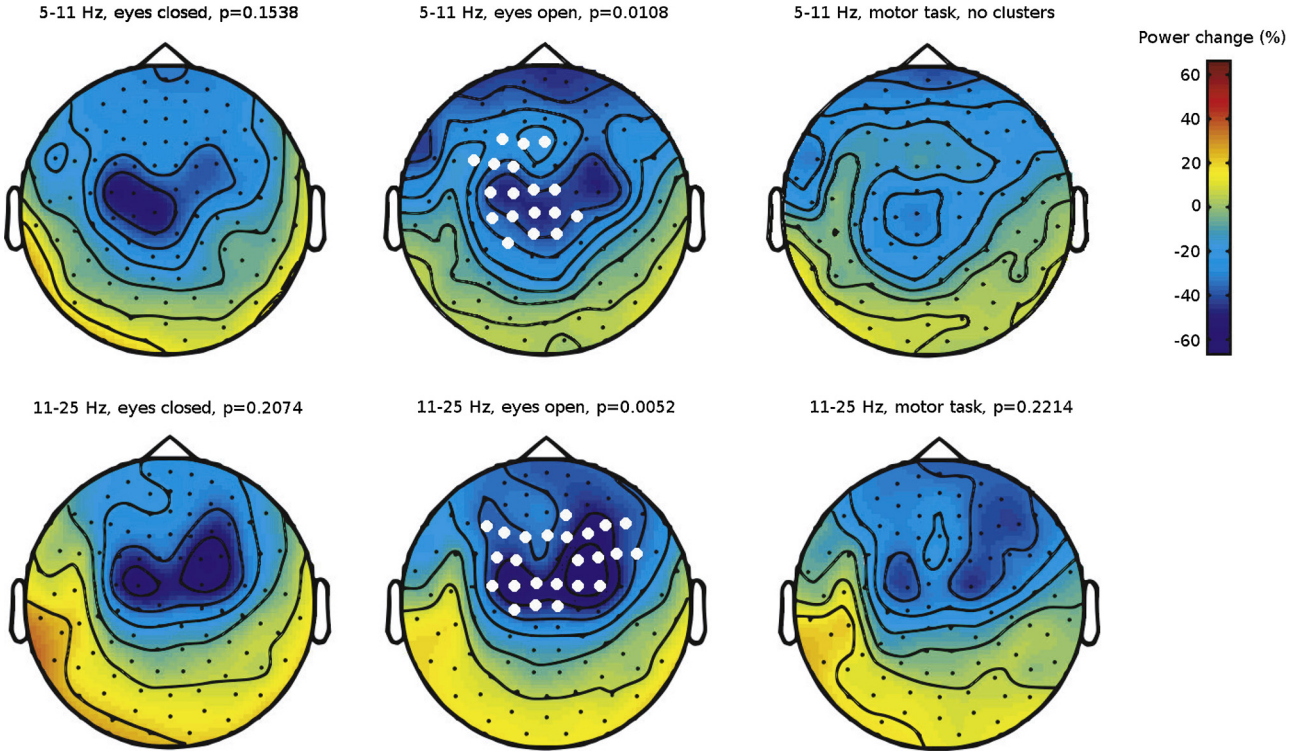

Fig. 2. Average relative power change between the DBS conditions for 5–11 Hz and 11–25 Hz during rest and wrist extension. The blue color denotes power decrease and red color power increase by DBS. The small black circles represent gradiometer pairs and the white dots represent a cluster with the highest power decrease ($p = 0.0108$ for 5–11 Hz and $p = 0.0052$ for 11–25 Hz). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

changes should be taken into account when analyzing the effects of DBS on the sensorimotor activity in PD patients.

Maximum CMC occurred over the sensorimotor area in the hemisphere contralateral to the extended hand, as reported previously (e.g [19].). The spontaneous activity suppression induced by DBS was more extensive, particularly in the frontal regions and may indicate contribution of supplementary motor areas in the effect of DBS (cf [17].).

4.2. Limitations of the study

DBS produces strong artifacts to MEG signals. DBS artifacts increase in power when DBS is on; instead, we observed a power decrease over the frontoparietal cortex. As DBS interference was suppressed by tSSS and notch filtering, an artifactual power decrease could be possible if the filtered DBS interference was correlated with brain activity. If the power decrease was purely artifactual, they would remain approximately the same in analysis of spontaneous data and the MEG during wrist extension. Instead, we observed weaker beta power during the wrist extension than in the spontaneous activity recording.

The MEG measurements were done first with DBS on and then, approximately 10 min later, with DBS off. At least three hours of STN DBS off is required to establish a steady DBS off state for efficacy studies [34]. About 50% of the total change has, however, been estimated to occur in 5 min after DBS is turned off [5]. Clearer changes could have occurred if the period between on and off states would have been longer, and if patients had been recorded in medication off-phase.

5. Conclusions

Sensor-level MEG of 16 PD patients with STN DBS revealed significantly decreased power in 5–25 Hz spontaneous activity at rest when DBS was turned on. This power decrease was the clearest in the bilateral frontoparietal areas and overlapped with the distribution of CMC. Our results support the notion that DBS alleviates motor symptoms in PD by reducing pathological synchrony in the sensorimotor network.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neulet.2018.06.041.

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