

Feasibility of magnetoencephalographic source imaging in patients with thalamic deep brain stimulation for epilepsy

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SUMMARY

Source localization of interictal spikes in patients with medically refractory epilepsy is the most common clinical application of magnetoencephalography (MEG). In recent decades, many patients with intractable epilepsy have been treated with various forms of neurostimulation, including thalamic deep brain stimulation (DBS). Patients with suboptimal seizure control after DBS might in some cases benefit from further investigations for resective epilepsy surgery, including MEG source imaging (MSI). We sought to determine the feasibility and accuracy of MSI in the setting of active thalamic DBS. Simultaneous EEG/MEG was obtained in a patient using an Elekta 306-channel MEG system, with high-frequency (100 Hz) DBS of the thalamic anterior nuclei cycling between on and off states. Magnetic artifacts associated with the DBS apparatus were successfully suppressed using the spatiotemporal signal space separation (tSSS) method. Electrical stimulation artifact was removed by standard digital low-pass filtering. Dipole source modeling results for spike foci in frontal and posterior temporal regions were comparable between stimulation on and stimulation off states, and the source solutions corresponded well to the localization of spikes documented by intracranial EEG. MSI is thus feasible and source solutions can be accurate when performed in patients with active thalamic DBS for epilepsy.

KEY WORDS: Deep brain stimulation, Magnetoencephalography, Source localization, Spatiotemporal signal space separation, Thalamus anterior nuclei.



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Noninvasive source localization of interictal spikes is the most common clinical application of magnetoencephalography (MEG), and MEG source imaging (MSI) is now of accepted benefit in the presurgical investigation of patients with medically intractable epilepsy.¹ In recent decades,

many patients with intractable epilepsy have been treated with various forms of neurostimulation, including thalamic deep brain stimulation (DBS).^{2,3} Patients with suboptimal seizure control after thalamic DBS might in some cases benefit from further investigations for resective epilepsy surgery, including MSI. It is thus of interest to know if DBS-induced electromagnetic artifacts preclude MSI, or if modern artifact suppression methods may render MSI feasible in the setting of active thalamic DBS.

Different artifact suppression methods have been used to enable successful MEG recordings in patients treated with DBS for Parkinson's disease or chronic pain.^{4–9} These methods have included beamforming,⁷ independent component analysis and rejection based on mutual information,⁹ or application of the spatiotemporal signal space separation (tSSS) algorithm.^{4–6,8} The latter method, first described by Taulu and Simola,^{10,11} is implemented within the Elekta Neuromag Maxfilter system (Elekta, Helsinki, Finland) and has been used to enable MSI in epilepsy patients treated

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with vagus nerve stimulation (VNS).^{12,13} We sought to determine the feasibility and accuracy of MSI in the setting of active thalamic DBS, using tSSS artifact suppression.

METHODS

Approval was obtained from the research ethics board of the University Health Network, Toronto, Ontario, Canada, for MEG studies in patients with DBS. Two patients with medically intractable epilepsy and continued disabling seizures despite thalamic DBS therapy were referred for MEG as part of repeat investigation for epilepsy surgery. In both patients, DBS electrodes (model 3387; Medtronic, Minneapolis, MN, U.S.A.) were situated bilaterally in the anterior thalamic nuclei,² with Activa or Kinetra neurostimulators (Medtronic) located subcutaneously in the subclavicular region. No interictal spikes occurred in one patient, despite more than 90 min of recording, and thus only the second (Kinetra) patient's case is presented in detail with respect to MSI.

Recordings were acquired using an Elekta Neuromag TRIUX 306-channel MEG system including 32 scalp electroencephalography (EEG) channels (Elekta); sampling frequency was 1,000 Hz. Recordings were obtained using clinical DBS parameter settings (4 V, 90 μ s, 100 Hz, 1–3+/5–7+ bipolar or 1-case+/5-case+ monopolar), with the exception that cycling on/off frequency was changed from 1 min on/5 min off to 1 min on/2 min off. Specifically, the pulse generator was programmed to automatically cycle through a period of active stimulation lasting 1 min, followed by a period of no stimulation lasting 2 min, followed by active stimulation for 1 min, followed by no stimulation for 2 min, and so on.

Artifact suppression using the default parameters of the tSSS algorithm implemented within the Elekta Maxfilter system (10-s time window, subspace correlation 0.980) was applied to the data once obtained. The tSSS algorithm first divides the measured signal into two parts (arising from mainly inside and mainly outside the MEG sensor array) using the signal space separation method, and then identifies temporally correlated signal components between the inside and outside (e.g., the magnetized DBS electrodes inside the brain and the wires and neurostimulator outside the sensor array) and excludes them from the data.¹⁰

Interictal spikes were visually identified in the raw EEG and tSSS artifact-suppressed MEG data (band-passed between 1 and 70 Hz) and grouped into different foci for spike averaging based on detailed analysis of each spike's morphology and associated EEG/MEG voltage/flux field topography, as previously described.^{14,15} MSI of individual and averaged spikes was performed using CURRY 6 (Abbotsford, Vic., Australia).¹⁴ Spike epochs were generated using a 1-s time window from –750 to +250 ms relative to the spike peak. Spikes occurring within 750 ms of another spike (or selected spike epoch) from the same focus were excluded (to permit uncontaminated epoching). Noise

level was estimated as the variance of the data in the signal from –750 to –250 ms before each individual or averaged spike. A 5- to 30-Hz band-pass filter, spherical forward model, and equivalent current (fixed coherent) dipole or distributed source (sLORETA) inverse models were used for MSI.

Case history

A 30-year-old patient with chronic cryptogenic medically intractable epilepsy. Normal cognition and brain MRI. Two previous MSI studies at other institutions at ages 14 and 21 years described multiple dipole source solutions for individual spikes in both hemispheres, mainly on the right, especially in the region of the right superior frontal gyrus. VNS initiated at age 17 was not associated with significant improvement, and over the next 5 years seizure-related falls gradually increased. Combined scalp/intracranial EEG investigation at age 22, sampling bilateral medial and lateral frontal cortices with subdural strip electrodes, showed, in addition to focal spikes, bilaterally synchronous 2.5-Hz frontal spike/wave complexes (Fig. S1) and low-amplitude fast ictal polyspike discharges involving both superior lateral frontal convexities. An anterior two-thirds callosotomy was performed, initially resulting in decreased falls, but total seizure frequency increased. The VNS neurostimulator was explanted and thalamic DBS initiated at age 24.

RESULTS

Magnetic artifact associated with the DBS apparatus, most prominent in low-frequency bands, contaminated the raw MEG signal, affecting magnetometers to a greater extent than planar gradiometers (Fig. 1, two left columns). Application of the tSSS algorithm to the data successfully removed the artifact (in both patients studied), allowing for visual interpretation of the background MEG signal and identification of interictal spikes (Fig. 1, two right columns). High-frequency stimulation artifact present during DBS on states was removed by standard digital low-pass filtering below 100 Hz (Fig. 1B).

Interictal spikes were recorded during two 30-min recording sessions obtained with active (1) bipolar and (2) monopolar cycling DBS. Spikes occurred most frequently over the right midfrontal region (F4 EEG maximum), less frequently over the right posterior basal temporal region (P10 EEG maximum), and least frequently over the left midfrontal region (F3 EEG maximum). The bilaterally synchronous frontal spike/wave discharges recorded during previous EEG investigations were not evident, presumably owing to the effects of the callosotomy; the posterior temporal spikes had not been documented in earlier investigations. Approximately 50% of the spikes recorded from each focus were selected for MSI, the remainder excluded because of their close (<750 ms) temporal proximity to other spikes or spike epochs from the same focus (see Methods). For

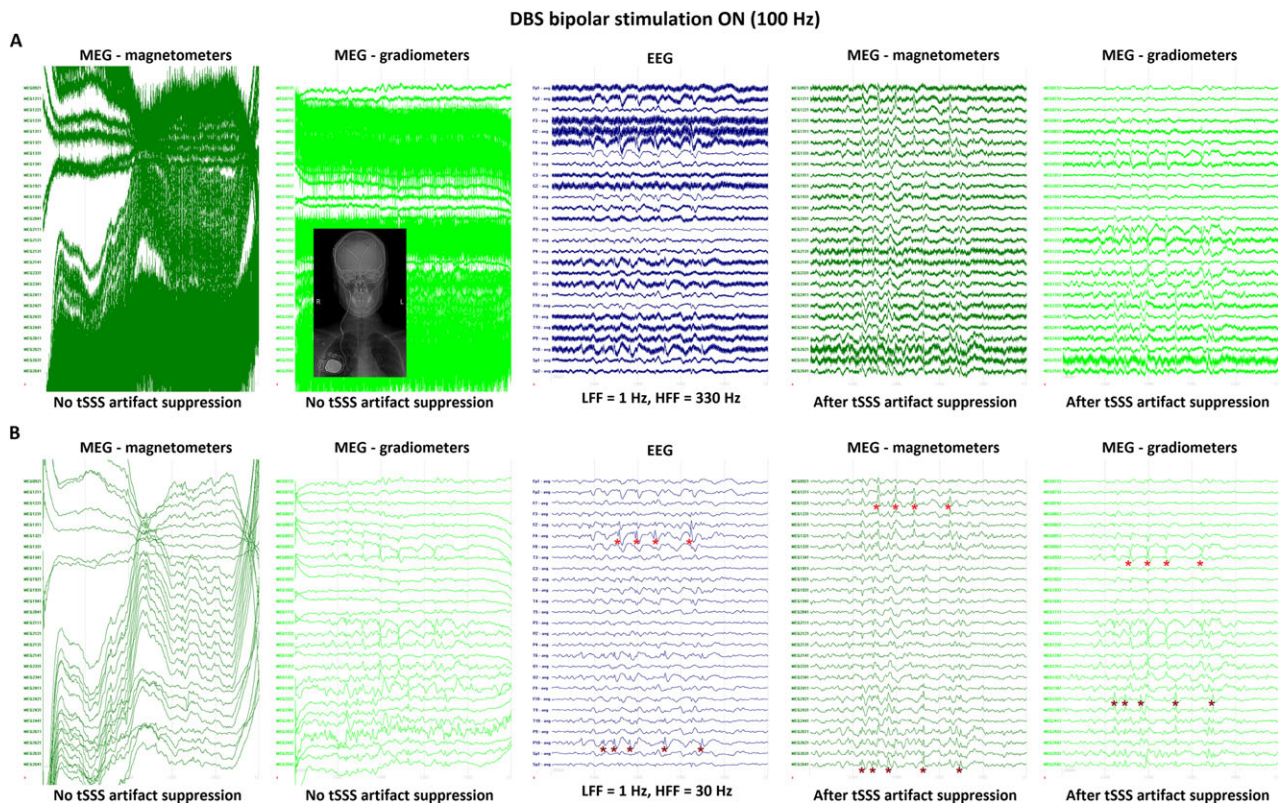


Figure 1.

Five seconds of EEG/MEG; runs of independent spikes over right frontal (red asterisks, EEG F4 > Fz, Fp2) and right posterior temporal (purple asterisks, EEG P10 > T6, O2) regions. **(A)** Low-frequency filter (LFF) 1 Hz; high-frequency filter (HFF) 330 Hz. **(B)** LFF 1 Hz; HFF 30 Hz. First column, 27 magnetometer channels, no tSSS artifact suppression. Second column, 27 planar gradiometer channels, no tSSS artifact suppression. Middle column, 27 EEG channels, common average reference. Fourth column, same 27 magnetometer channels as first column, after tSSS artifact suppression. Fifth column, same 27 gradiometer channels as second column, after tSSS artifact suppression. Inset: X-ray image of patient's implanted thalamic DBS electrodes, connecting leads, and right subclavicular neurostimulator.

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example, only the fourth of the marked right frontal spikes and the fourth of the marked right posterior temporal spikes shown in Fig. 1 would have been selected for modeling. Notwithstanding, most selected spikes occurred as isolated discharges: the brief runs of spikes presented in Fig. 1 were chosen to maximally illustrate the effects on MEG spikes of tSSS artifact suppression and low-pass filtering.

MSI (using the combined 306-channel data from the planar gradiometers and the magnetometers) of spikes from all three independent foci returned plausible source solutions: for the two frontal lobe foci, solutions obtained for averaged spikes corresponded well to the superior lateral frontal convexity areas previously documented by intracranial EEG to be involved at the time of simultaneously recorded scalp EEG frontal spikes and spike/wave discharges. Dipole source solution coordinates (from the center of the spherical head model) for averaged spikes recorded with the DBS neurostimulators off were: $x = 18.5$ mm, $y = 47.3$ mm, $z = 77.2$ mm (right superior frontal sulcus, explained variance [V] = 92.0%, number of spikes [n] = 19); $x = 34.7$ mm, $y = -36.0$ mm, $z = 30.2$ mm (right

posterior fusiform gyrus, V = 96.4%, n = 18); and $x = -23.9$ mm, $y = 42.0$ mm, $z = 62.4$ mm (left middle frontal gyrus, V = 76.9%, n = 9).

Sufficient spikes ($n \geq 8$) occurred during stimulation on periods to permit comparison of MSI results between stimulation on and stimulation off states for the right frontal focus (during bipolar DBS) and the right posterior temporal focus (during monopolar DBS). Fig. 2 shows the dipole mapping and sLORETA source localization results for the right frontal focus, comparing averaged spike source solutions for spikes acquired during bipolar DBS on and off states. The results show no clinically relevant differences in MSI localizations ($\Delta x = 1.2$ mm, $\Delta y = 3.8$ mm, $\Delta z = 1.5$ mm for dipole sources), i.e., modeling was not adversely affected by the electrical stimulation.

Modeling of individual spikes was associated with some spatial scatter of dipole source solutions, as compared to modeling averaged spikes from the same focus, as expected,^{14,15} with no difference between stimulation on and off results (Fig. S2).

Statistical analyses of the dipole source locations and orientations, performed by randomly shuffling spikes from

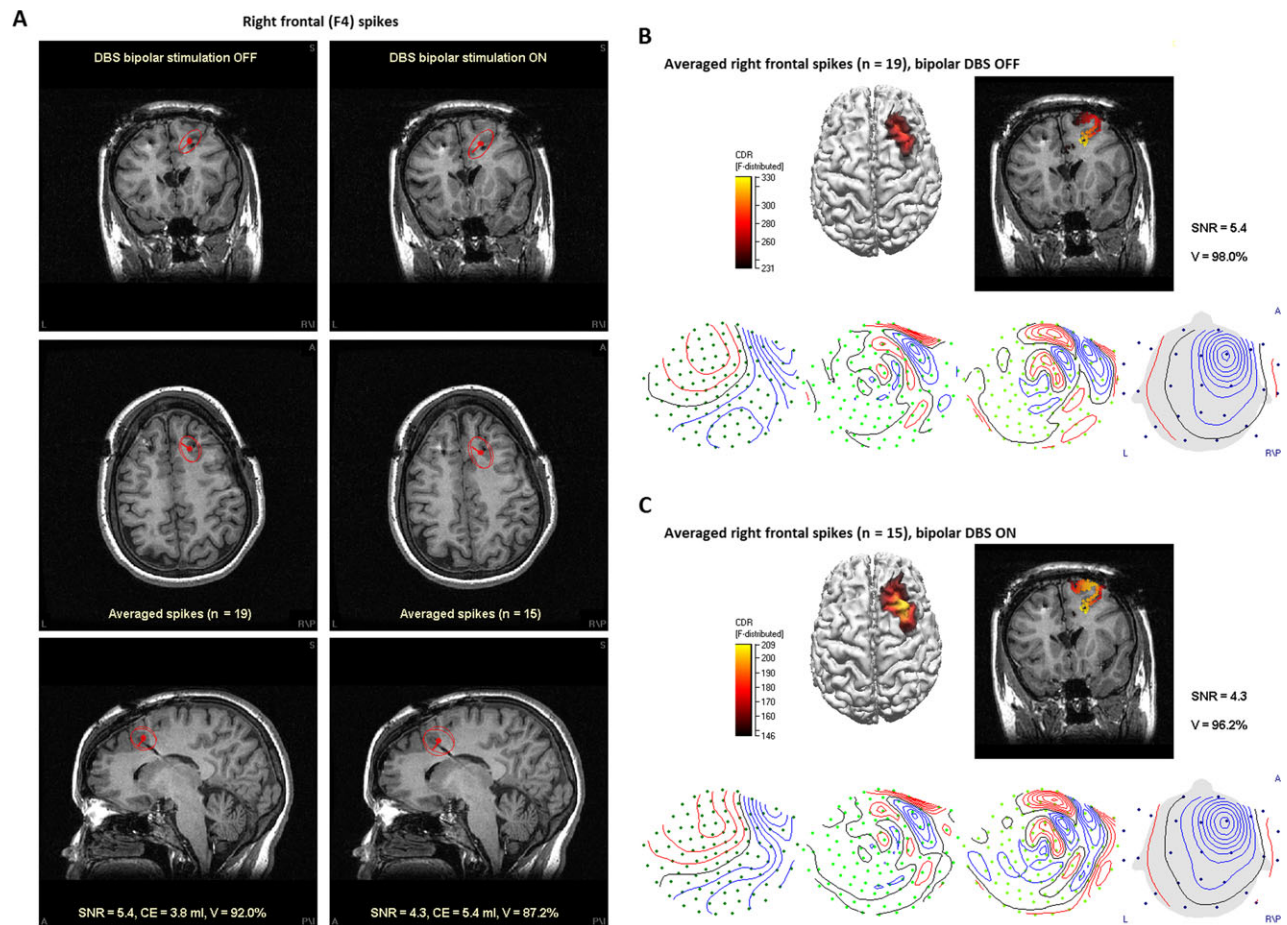


Figure 2.

(A) Dipole mapping source solutions and surrounding confidence ellipsoids for the right frontal spike focus, averaged spikes, bipolar DBS off (left, $n = 19$) and on (right, $n = 15$). (B) sLORETA distributed source solution, bipolar DBS off, averaged ($n = 19$) spikes (top, cortical constraint, rotating, 20-mm extension, clip below 70%), flux/voltage topographic plots (bottom) for magnetometers (left), orthogonal planar gradiometers (middle) and EEG (right). (C) sLORETA distributed source solution, bipolar DBS on, averaged ($n = 15$) spikes (top, cortical constraint, rotating, 20-mm extension, clip below 70%), flux/voltage topographic plots (bottom) for magnetometers (left), orthogonal planar gradiometers (middle), and EEG (right). SNR, signal-to-noise ratio; CE, confidence ellipsoid; V, explained variance; CDR, current density reconstruction.

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both states (DBS on and off) into two groups, confirmed no difference in MSI results between stimulation on and off states (Data S1). MSI solutions for averaged spikes from the right posterior temporal focus, comparing monopolar DBS on and off states, likewise showed no clinically relevant dipole source localization differences ($\Delta x = 0.6$ mm, $\Delta y = 10.0$ mm, $\Delta z = 7.0$ mm; Fig. S3).

The MSI results obtained using gradiometer data alone, and magnetometer data alone, are shown for the right frontal focus in the Table S1. For both DBS on and off states, dipole mapping using just the gradiometer data returned source solutions with lower V values, but tighter confidence ellipsoids (CEs), as compared with solutions obtained using just the magnetometer data. Compared to the source localizations obtained using the combined data, modeling just the gradiometer

data returned solutions within 5 mm of the combined results in all three planes. The magnetometer source solutions were slightly (2–10 mm) deeper and more medial than either the combined data or the gradiometer-alone localizations (and further from the intracranial EEG localization).

Given the inherent advantages of MEG over EEG for source modeling in the setting of multiple skull defects, we did not initially perform EEG source imaging (ESI) in this patient. However, a reviewer requested that this be done, and dipole mapping results for the right frontal focus are shown in the Table S1. Using the same band-pass filter settings and noise estimation methods described for MSI, the ESI source localizations were lateral, anterior, and more than 20–30 mm deep to all of the MSI solutions, with much larger CEs.

A reviewer of the original version of this paper commented that spikes were clearly visible in gradiometer channels after low-pass filtering—without tSSS artifact suppression—and asked whether the artifact suppression was absolutely necessary; i.e., could MSI be performed successfully on the MEG data after only simple filtering? Using just the gradiometer data (and methods otherwise identical to those used for the artifact-suppressed data), MSI solutions for averaged spikes from the right frontal focus were located within 2–8 mm of the solutions obtained from modeling the artifact-suppressed data (albeit with lower V values and much larger CEs; Table S1). Reasonable source solutions could not, however, be obtained using the magnetometer data in the absence of tSSS artifact suppression (Table S1).

DISCUSSION

The results presented here demonstrate that MSI is feasible and that source solutions can be accurate in patients receiving anterior thalamus DBS for epilepsy. Consistent with previous studies, magnetic artifacts associated with the DBS apparatus were most evident in low-frequency bands^{5,6} and most evident in magnetometers. Application of tSSS effectively suppressed the artifacts and did not appear to alter the visible MEG signal, in the frequency bands of clinical interest, when compared to the simultaneous EEG signal. The implementation of tSSS within the Elekta Neuronavigation Maxfilter system rendered DBS artifact suppression simple using this MEG system. We cannot comment on the effectiveness of other DBS artifact suppression methods designed for use with different MEG systems,^{7,9} but these too may prove to be effective for MSI in epilepsy.

In the EEG signal, electrical stimulation artifact was much more evident with 100-Hz monopolar DBS, as compared to bipolar DBS; however, the differences were not marked in visual analysis of the MEG signal. For MSI of interictal epileptiform discharges, low-pass filtering was sufficient to remove the high-frequency stimulation artifact. In principle, such low-pass filtering may be insufficient to deal with aliased lower frequency artifact components arising during analog/digital conversion of the high-frequency electrical stimulation signal, which could have important effects on, e.g., spectral-based analyses of low-amplitude oscillatory signals in MEG and EEG.¹⁶ Nevertheless, for MSI of interictal spikes (which, in contrast to low-amplitude oscillations, are transients two to five times higher in amplitude than background), it would appear that these aliasing effects can be safely ignored. To optimize the signal-to-noise ratio for source localization, multiple spikes from the same focus must be averaged,^{14,15} decreasing the contribution of any such artifact present in individual epochs to the final signal to be analyzed. And even in the absence of spike averaging, the possible presence of aliased stimulation artifacts in spike epochs selected from DBS on periods had no discernible effect on MSI results when compared to the

solutions returned for spike epochs selected from DBS off periods, arguing that more sophisticated filtering is not necessary for MSI of spikes in patients with DBS for epilepsy.

Finally, although demonstrated here in only one patient, the observation that simple filtering of planar gradiometer MEG data—even without tSSS artifact suppression—may be sufficient to obtain MSI solutions similar (albeit less robust) to those obtained from modeling the tSSS artifact-suppressed data supports (1) the noise reduction benefits of orthogonal planar gradiometer sensors, and (2) a lack of adverse effects of the tSSS method on the MEG signal, at least for the purposes of MSI in epilepsy.

DISCLOSURE

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Bilaterally synchronous 2–2.5 Hz spike/wave discharges recorded over both lateral frontal convexities during simultaneous scalp/intracranial EEG investigation.

Figure S2. (*Left*) Dipole mapping source solutions for the right frontal spike focus, single spikes (with $V > 70\%$, $n = 13$, yellow), averaged ($n = 8$) spikes (spikes 1–8, 5–12, 8–15, 12–19, cyan), and grand average ($n = 19$, red), bipolar DBS off. (*Right*) Dipole mapping source solutions for the right frontal spike focus, single spikes (with $V > 70\%$, $n = 12$, yellow), averaged ($n = 8$) spikes (spikes 1–8, 5–12,

8–15, every second spike from 1–15, cyan), and grand average ($n = 15$, red), bipolar DBS on.

Figure S3. Dipole mapping source solutions for the right posterior temporal spike focus, averaged spikes, monopolar DBS off (*top*, $n = 18$) and on (*bottom*, $n = 8$). (**A**) Flux/voltage topographic plots for magnetometers (*left*) and EEG (*right*). (**B**) Dipole source solutions and surrounding confidence ellipsoids.

Table S1. Best-fit dipole source solution parameters, right frontal spike focus, DBS OFF versus ON, with and without tSSS artifact suppression.

Data S1. Statistical analyses of the similarity of dipole source locations and orientations between DBS ON and OFF conditions.