Influence of magnetic source imaging for planning intracranial EEG in epilepsy

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ABSTRACT

Background: Magnetic source imaging (MSI) is used routinely in epilepsy presurgical evaluation and in mapping eloquent cortex for surgery. Despite increasing use, the diagnostic yield of MSI is uncertain, with reports varying from 5% to 35%. To add benefit, a diagnostic technique should influence decisions made from other tests, and that influence should yield better outcomes. We report preliminary results of an ongoing, long-term clinical study in epilepsy, where MSI changed surgical decisions.

Methods: We determined whether MSI changed the surgical decision in a prospective, blinded, crossover-controlled, single-treatment, observational case series. Sixty-nine sequential patients diagnosed with partial epilepsy of suspected neocortical origin had video-EEG and imaging. All met criteria for intracranial EEG (ICEEG). At a surgical conference, a decision was made before and after presentation of MSI. Cases where MSI altered the decision were noted.

Results: MSI gave nonredundant information in 23 patients (33%). MSI added ICEEG electrodes in 9 (13%) and changed the surgical decision in another 14 (20%). Based on MSI, 16 patients (23%) were scheduled for different ICEEG coverage. Twenty-eight have gone to ICEEG, 29 to resection, and 14 to vagal nerve stimulation, including 17 where MSI changed the decision. Additional electrodes in 4 patients covered the correct: hemisphere in 3, lobe in 3, and sublobar ictal onset zone in 1. MSI avoided contralateral electrodes in 2, who both localized on ICEEG. MSI added information to ICEEG in 1.

Conclusion: Magnetic source imaging (MSI) provided nonredundant information in 33% of patients. In those who have undergone surgery to date, MSI added useful information that changed treatment in 6 (9%), without increasing complications. MSI has benefited 21% who have gone to surgery. *Neurology*® 2008;71:990-996

GLOSSARY

2nd STEP = changed second step; **ADD** = MSI decision to add electrodes; **BiF** = bifrontal; **Bil** → **Uni** = bilateral to unilateral; **Change ICEEG** = MSI changed the ICEEG decision as indicated; **Class** = postoperative outcome class; **Dec** → **VNS** = declined surgery and had VNS; **Decl** = declined ICEEG and surgery; **Defr** = deferred surgery, pending ICEEG; **ECOG** = electrocorticography; **F** = frontal; **FU** = postoperative follow-up after focal excisional surgery; **ICEEG** = intracranial EEG; **ICEEG Loc** = intracranial EEG localization; **ICEEG** → **VNS** = MSI changed decision from ICEEG to VNS; **LAT** = left anterior temporal lobectomy; **LF** = left frontal; **LT** = left temporal; **LTm** = left mesial temporal; **LTml** = left temporal both mesial and lateral; **LTps** = left temporal lateral posterior; **MSI** = magnetic source imaging; **MSI Lat** = MSI lateralization; **MSI Lob** = MSI lobar localization; **MSI Loc** = MSI sublobar localization; **Op** = surgical intervention; **Pdg-Surg** = pending excisional surgery; **Pdg-VNS** = pending VNS; **RAT** = right anterior temporal lobectomy; **RC** = right central; **Red %** = percentage reduction of seizures by surgery; **Remis** = spontaneous remission of seizures, no surgery; **RF** = right frontal focal excision; **RFp** = right frontopolar focal excision; **ROp** = right opercular; **ROpRT** = right opercular and right temporal regional ICEEG onset and multilobar resection; **RTm** = right mesial temporal; **RTml** = right temporal both mesial and lateral; **T** = temporal; **VEEG** = video-EEG; **VNS** = vagal nerve stimulation.

Magnetic source imaging (MSI) is accepted as clinically useful in presurgical evaluation of intractable partial epilepsy¹⁻¹² and in mapping hand primary somatosensory cortex for preoperative evaluation of brain tumors.^{13,14} Recent efforts have extended MSI to language mapping.¹⁵⁻¹⁷ MSI is useful in epilepsy, but information is indirect. MSI usually records interictal

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spikes and then models their sources with single dipoles. Spike location is near the zone of seizure origin in most patients, but the correlation is not exact.^{1,18-20} Recent assessments of MSI have indicated a lack of prospective, blinded, controlled, intention-to-treat studies with large numbers.²¹ We evaluated MSI utility in a prospective, blinded observational case series to test the hypothesis that MSI influences decision making and results in better outcomes. All patients who had MSI were followed up by using a basic intention-to-treat approach.

A MEDLINE search with key words “magnetoencephalography or MEG or magnetic source imaging or MSI” and “epilepsy” and “surgery” identified 224 citations. Of these, 182 were reviews, case reports, or articles about language/sensation, tumors, or technical issues. The remaining 42 reported series with new MSI data for presurgical evaluation. Thirty-nine studies used MSI spike dipoles, with patient numbers from 4 to 455. Three were prospective or analyzed with a prospective intention,^{10,22,23} and two were blinded.^{10,24} One of these was prospective and blinded with crossover control and used MSI to modify surgical decisions.¹⁰ Intention to treat was not noted in the studies.

Although most studies showed a benefit of MSI, yield ranged widely, from 5% to 35%. Variability in the benefit of MSI is expected because of various presurgical video-EEG protocols for partial epilepsies not of mesial temporal origin^{25,26}; however, more precise determination of this yield with a standard protocol seemed warranted and motivated this study. Our two underlying hypotheses were that MSI influences planning for intracranial EEG (ICEEG) and that this influence results in better outcomes.

METHODS Patient recruitment strategy. We prospectively studied all patients with medically intractable partial epilepsy who were referred to our comprehensive epilepsy center for presurgical evaluation over a 2-year period from February 2004 until February 2006 and did not meet “skip” criteria^{18-20,27} for proceeding directly to temporal lobectomy. Thus, all patients who required ICEEG were studied.

Inclusion and exclusion criteria. Inclusion criteria were 1) partial epilepsy, 2) failure of three antiepileptic drugs to control socially disabling seizures over 2 years, 3) five or more spikes captured on MSI, 4) ability to give informed consent, and 5) age 5 to 70 years. Exclusion criteria were 1) malignant

tumor, 2) severe medical illness, 3) moderately severe developmental delay (suggesting nonlocalized epilepsy), and 4) active psychosis.

Patient comparisons. This was an observational case-series study. All patients received care based on the accepted presurgical protocol with MSI. Patients were not randomly assigned to receive or not receive MSI, because MSI is an accepted procedure in presurgical evaluation and it was believed unethical to deny patients this test. The key questions were to what degree MSI changes surgical decision making and outcomes. The key comparison was between the surgical conference decisions before and after presentation of the MSI results.

Patient demographics. There were 69 patients who met criteria with medically intractable partial seizures or partial secondarily generalized seizures. Patients were aged 8 to 66 years. Informed consent was obtained. See appendix e-1 on the *Neurology*[®] Web site at www.neurology.org.

MSI procedure. As previously reported,^{1,28,29} we used a 100-channel, 68-sensor site whole-cortex neuromagnetometer with third-derivative synthesized gradiometers in a shielded chamber. At least five spikes were obtained to ensure reproducibility and to visualize clusters. Five spikes was selected so that the large majority of the patients could be studied, because some patients had rare spikes. Repeat studies were required in some. Band pass was direct current to 300 Hz, with a digitization rate of 1,250 Hz and off-line filter 1 to 70 Hz. Artifact was visually identified and eliminated. All spikes were agreed on by two observers (W.W.S. and N.L.), one a board-certified electroencephalographer (W.W.S.). The spikes were first selected by N.L. and then, after the first decision was made, verified by W.W.S. as the MSI was presented for the second decision. Only spikes agreed on by both N.L. and W.W.S. were used for the MSI decision. Interrater reliability/concordance for spike recognition was 95%. The data were analyzed with the equivalent current dipole model coregistered to MRI. See appendix e-2.

MSI system accuracy. We tested accuracy of the MSI system by using phantoms, evoked responses, and afterdischarges at subdural electrodes during ICEEG. The error was 1.4 ± 0.9 mm in phantoms.²⁸ Evoked responses were reproducible between systems within 2.4 mm for evoked responses and within 8.9 mm for language between our system and 151- and 275-channel systems.^{15,17} The error between the center of stimulated subdural electrodes and 13 afterdischarge dipoles in two patients was 8.0 ± 1.7 mm (SEM 0.46 mm).^{28,29} This confirmed that there was 95% confidence that the mean error was within 9 mm for repetitive spikes of afterdischarges. See appendix e-3.

Noninvasive video-EEG and imaging protocol. Details of the video-EEG and imaging protocol have been described before.^{1,18,30} Each patient had typical seizures on standard inpatient video-EEG. Neuropsychometric and sodium amytal testing was performed. Metabolic PET and ictal SPECT were performed when indicated. A patient met “skip” criteria³¹ for standard anterior temporal lobectomy if the video-EEG showed a focal temporal onset pattern,³² imaging showed ipsilateral mesial temporal sclerosis on MRI or focal temporal hypometabolism on PET, the patient passed the amytal test, and there were no conflicting data. Patients with a static lesion larger than 1.0 cm had “lesionectomy-plus” if the EEG was lateralizing and there were no conflicting data. All others were recommended for ICEEG, either depth electrodes or subdural

Figure 1 Flowchart of patient decision algorithm

The pre-magnetic source imaging (MSI) decision was blinded to MSI. The patients were assigned to one of three treatments. The blind was then broken, and the MSI information was presented. Then a post-MSI decision was made, and the patients were reassigned to one of three treatments. The post-MSI treatments are primed. One-third of the patients were reassigned to a different treatment by the post-MSI decision. VEEG = video-EEG; ICEEG = intracranial EEG; VNS = vagal nerve stimulation.

grids, if there was a reasonable hypothesis of a focal zone of seizure origin.

Epilepsy conference. The bimonthly epilepsy conference was attended by a clinical team that included a neurosurgeon, three neurologists, a neuropsychologist, and a nursing staff. Figure 1 shows the flowchart of decision making. Two decisions were made: the pre-MSI decision and the post-MSI decision. Each decision was documented in a written description and diagram on a printed form, similar to a procedure described previously.¹⁰ For the first decision, all routine presurgical information from the video-EEG and imaging protocol was presented. The clinical team was blinded to MSI at this time. The pre-MSI decision was made on ICEEG, excisional surgery, or vagal nerve stimulation (VNS) and was documented. For the second decision, the MSI was then presented by a physician-scientist who had analyzed the MSI but did not vote (D.T.). A second decision was then made either to alter or not to alter the first surgical decision in view of the information from MSI and was documented. Where MSI showed a location different from that indicated by the standard protocol, a decision was made to add intracranial electrodes over the MSI-indicated location. Additional electrodes were diagrammed over the location with the densest MSI spike cluster.

Blinding. All members of the conference who voted for the pre-MSI surgical decision were blinded to the MSI results. All neurologists, including the one who rated postoperative surgical outcomes, did not know the MSI results at the time the pre-MSI decision was made. If any voting member became inadvertently aware of the MSI results, the member was ex-

cluded from voting in the pre-MSI decision or discussing the case before the pre-MSI decision.

Outcome measures: ICEEG localization and postoperative seizure reduction. There were two outcome measures. The first was ICEEG localization, with which MSI was compared. The second was postoperative seizure reduction. Patients had standard or tailored focal resections. Postoperative seizure frequency at 3 months, 6 months, and 1 year were obtained for all patients by personal contact with the patient and family by one of us (W.W.S.), in clinic follow-up visits in the large majority of patients or by phone interviews in some, when the patient lived afar and was unable to return. Outcome results were ranked by the Engel classification.¹⁸⁻²⁰

Analysis. There were 69 patients who met criteria for analysis and for decision making. All patients were followed with a basic intention-to-treat approach to avoid any bias in dropping or excluding patients. All patients are reported based on their original group, MSI changing or MSI not changing the decision. What occurred at all points during the study is reported.

RESULTS MSI changed the surgical decision in 23 patients (33%), shown in table 1. In the other 46, MSI gave information similar to the standard noninvasive video-EEG and imaging protocol. Table 1 shows that MSI changed the decision to additional subdural strip electrodes in 9, from no surgery to ICEEG in 2, from excision to ICEEG in 2, from ICEEG to vagal nerve stimulator in 4, and from bilateral to unilateral ICEEG in 3. MSI changed the second step in presurgical evaluation in 3 and reduced tests in 1. See appendix e-4.

Outcomes. Twenty-eight patients have had ICEEG, 29 have had focal resections, and 14 have had VNS. Of those where the MSI changed the decision, 10 have had focal resections and 6 have had VNS. The mean follow-up after resection is 17 months; only 1 patient has less than 6 months. MSI has clearly benefited 6 patients, which represents 9% of all patients entered in the series and 21% of patients who have gone to resection to date. In these 6 patients, MSI influenced decisions by eliminating bilateral electrode coverage in 2 who are seizure free (nos. 7 and 52), indicating correctly a frontal seizure zone not apparent on the first ICEEG in 1 who is seizure free (no. 33), reducing tests in 1 who is seizure free (no. 20), and prompting ICEEG in 2 patients who have class II and III outcomes (nos. 18 and 49).

Illustrative case. Patient 33 had right frontopolar MSI spike dipoles (figure 2A). Scalp EEG showed right temporal onsets with interictal spikes over the right temporal lobe and right prefrontal region. Depth electrodes with a strip over the MSI spike cluster showed right mesial temporal ictal onset but rapid propagation within 10 seconds to the right frontal depth and strip. He underwent right anterior temporal lobectomy with gliosis in the resected specimen. Seizures recurred at 5 months, with the same preoperative frequency of five monthly. Repeat MSI showed a similar prefrontal spike dipole cluster (fig-

Table 1 Patients in whom MSI changed the surgical decision

Sequential patient no.	Years	Change ICEEG	ICEEG	ICEEG Loc	MSI Lat	MSI Lob	MSI Loc	Op	FU, mo	Red %	Class
2	36	ADD						Remis			
3	28	ADD						Decl			
7	22	Bil → Uni	Grid	LTm	L	T	LT	LAT	43	100	I
10	45	ADD	Strips	LTm	L	F	LF	LAT	20	100	I
11	38	ADD	Decl					Decl			
12	20	ADD	Grid	LTm	L	T	LTps	LAT	21	100	I
18	42	2nd STEP	Grid	RF	R	F	RFp	VNS/RF	28/8	15/93	III
20	8	Fewer tests	Grid	LTm	L	T	LTml	LAT	28	100	I
22	32	ADD						Dec → VNS			
26	19	No surgery → ICEEG						Dec → VNS			
29	29	2nd STEP	ECoG	RTm	R	T	RTml	RAT	13	100	I
33	22	ADD	Depth/Grid	RTm/RFp	R	F	RFp	RAT/RFp	16/13	0/100	I
41	29	ICEEG → VNS						VNS			
43	45	ICEEG → VNS						VNS			
45	38	Bil → Uni						Defr			
49	21	No surgery → ICEEG	Grid	ROpRT	R	Op	ROp	ROpRT	6	95	II
50	28	ADD	Decl					Decl			
52	56	Bil → Uni	Strips	LT	L	F	LF	LAT	3	100	—
64	26	ICEEG → VNS, 2nd	PDG					VNS			
65	34	Excision → ICEEG	PDG		R	C	RC	Pdg-Surg			
66	40	Excision → ICEEG	Decl					Decl			
68	19	ADD	ECoG	RF	B	F	BiF	RF	14	89	III
69	10	ICEEG → VNS						Pdg-VNS			

MSI = magnetic source imaging; Change ICEEG = MSI changed the ICEEG decision as indicated; ICEEG = intracranial EEG; ICEEG Loc = intracranial EEG localization; MSI Lat = MSI lateralization; MSI Lob = MSI lobar localization; MSI Loc = MSI sublobar localization; Op = surgical intervention; FU = postoperative follow-up after focal excisional surgery; Red % = percentage reduction of seizures by surgery; Class = postoperative outcome class; ADD = MSI decision to add electrodes; Remis = spontaneous remission of seizures, no surgery; Decl = declined ICEEG and surgery; Bil → Uni = bilateral to unilateral; LTm = left mesial temporal; T = temporal; LT = left temporal; LAT = left anterior temporal lobectomy; F = frontal; LF = left frontal; LTps = left temporal lateral posterior; 2nd STEP, 2nd = changed second step; RF = right frontal focal excision; RFp = right frontopolar focal excision; VNS = vagal nerve stimulation; LTml = left temporal both mesial and lateral; Dec → VNS = declined surgery and had VNS; ECoG = electrocorticography; RTm = right mesial temporal; RTml = right temporal both mesial and lateral; RAT = right anterior temporal lobectomy; ICEEG → VNS = MSI changed decision from ICEEG to VNS; Defr = deferred surgery, pending ICEEG; ROpRT = right opercular and right temporal regional ICEEG onset and multilobar resection; ROp = right opercular; — = follow-up too short to conclude outcome; PDG = pending; RC = right central; Pdg-Surg = pending excisional surgery; BiF = bifrontal; Pdg-VNS = pending VNS.

ure 2B). The distance between the average localization of the first MSI and the second MSI was 0.78 cm, within the localization error for afterdischarge spikes. Subsequent grid electrodes showed seizure onset in the right prefrontal region near the location of the MEG spike dipole cluster. The second resection was in the right frontal lobe, showed gliosis, and rendered the patient seizure free at 13 months.

Statistical and power analysis. The decision was changed by MSI in 33% of patients (23/69). The SEM of this proportion/percentage was 5.7%.³³ Therefore, there was 95% confidence that, of the total population of patients, at least 22% would have a decision change by MSI, with use of this protocol.

This is a clinically meaningful proportion of patients influenced by a new diagnostic test.

Table 2 shows the number of pre- and post-MSI decisions in the three main categories of surgical treatment: ICEEG, surgery without ICEEG, and VNS. There was obviously no significant difference in the numbers recommended for ICEEG. Most changes occurred in the surgery without ICEEG and VNS categories. These two categories were analyzed separately in a 2 × 2 table. This exploratory analysis showed a trend ($\chi^2 = 2.60$, $p = 0.10$, $df = 1$), toward more VNS decisions and fewer surgery without ICEEG decisions. This warrants further investigation in a larger sample.

Figure 2 Patient 33: MSI added information to ICEEG

These figures show the actual magnetic source imaging (MSI) data presented at the conferences. (A) First MSI, before intracranial EEG (ICEEG) and before first surgery. The MSI shows a cluster of spike dipoles in the right prefrontal region. MRI in top row: Left to right: Axial, coronal, and sagittal images. Bottom left: Typical spike in MEG. Calibrations: 10 pT, 270 msec. Bottom right: Isocontour maps and butterfly plot of tracings: Blue magnetic flux exiting head, red magnetic flux entering head. MRIs are radiology convention (with left at right of image); spike tracings and MEG map are electrophysiology convention (left at left). (B) Second MSI 18 months later, after first ICEEG and first surgery of right anterior temporal lobectomy (visible on sagittal section), but before second ICEEG and second surgery of right frontal resection. MSI shows similar cluster of spike dipoles in right prefrontal region. Figure setup same as in A. Calibrations: 12 pT, 404 msec.

Postoperative seizure outcomes were compared between the group where MSI changed the decision vs the group where MSI did not. In the first group, outcomes were, by class: I = 6 patients, II = 1 patient, III = 2 patients, IV = none. In the second group, outcomes were, by class: I = 11 patients, II = 4 patients, III = 2 patients, IV = 2 patients. There were no class IV patients in the group where MSI changed the decision, but this difference was not above chance with this study size ($p = 0.31$, χ^2). There was no difference in the percentage of patients who ultimately went to focal excisional surgery: 10/23 vs 19/46 (χ^2 , $p = 0.60$).

In 3 patients where MSI changed the decision, the observed outcomes were clearly improved with

the MSI to class I, II, and III in patients 33, 49, and 18, respectively, compared with the very likely class IV outcomes expected to occur without MSI. Patient 33, without MSI strongly indicating the frontal lobe, would not have had further ICEEG in our center. Patient 18 failed VNS but instead of callosotomy as the second step, based on MSI, he went to ICEEG, frontal resection, and class III. Because callosotomy does not help but often worsens partial seizures, we believe that MSI improved his case. Patient 49 went from no surgery to, based on MSI, ICEEG and resection with class II. Without surgery, he would have been unimproved. Without surgery, even with VNS, it is unlikely that patients will obtain a class III outcome. The MSI influence thus led to class I, II, or III in all 9 patients where MSI changed the decision, vs the expected 6 of 9 patients improved and 3 patients class IV. This difference is above chance ($p = 0.03$, χ^2).

Power analysis was performed to determine the required patient number to test with significance the hypothesis that the MSI changed the decision in the proportions given in table 2. The largest difference was the decrease in the surgery without ICEEG category: from pre-MSI 13/69 (proportion = 0.19) to post-MSI 7/69 (proportion = 0.10). To test for a difference of 0.10 between these proportions for the focused hypothesis that fewer patients went to surgery without ICEEG after MSI presentation, for a

Table 2 Pre- and post-MSI decisions in three main categories

	Pre-MSI	Post-MSI
ICEEG	45	47
Surgery without ICEEG*	13	7
Vagal nerve stimulation	8	12

*Focal excision without intracranial EEG (ICEEG), i.e., going directly to surgery without intracranial EEG recording. Because some patients were recommended for no further evaluation, the total in each of the decision columns is less than 69 for the three main categories analyzed. MSI = magnetic source imaging.

confidence level of $\alpha = 0.05$ (one-sided) with a power = 0.80 ($\beta = 0.20$), would require 175 patients enrolled in the study, each tested before and after MSI.³⁴

The results from this study can, however, give an estimate of the likely range of differences. For the present sample size of 69, a power analysis shows that a difference of proportions of 0.20 would have been detected with $\alpha = 0.05$ (two-sided) and power = 0.80 ($\beta = 0.20$).³⁴ Because such a difference was not detected, the difference in proportions thus is likely less than approximately 0.20.

DISCUSSION This study showed that MSI influenced ICEEG planning in one-third of all patients and was useful in a significant number of complicated epilepsy patients who require ICEEG, confirming our two underlying hypotheses. A benefit was seen in 9% of all patients, including 21% of those who have gone to surgery. MSI agreed with standard presurgical recommendations in two-thirds and added useful information in 26% of the remaining third. Based on these findings and the power analysis that the largest difference in proportions for a focused test in a subset of patients would likely be less than approximately 0.20, it is reasonable to expect that MSI may benefit approximately 10%, and up to 20% of patients. This estimate is in the middle range of 5% to 35% seen in the literature and consistent with a prior publication.¹⁰

An unexpected finding was that MSI added information to ICEEG (patient 33). The most parsimonious explanation was a focal seizure zone restricted to the frontal lobe, which was not detected by the first ICEEG, even with a directed frontal strip. This also could represent a multilobar seizure zone, in temporal and frontal lobes, with the most active onset from the temporal but with a residual frontal zone of seizure origin that became apparent after the temporal lobectomy. Without the MSI study, the approach at our center after unsuccessful surgery would have been VNS. Thus, MSI was instrumental in obtaining a class I outcome. See appendix e-5.

MSI benefitted the other patients by changing the overall surgical decision. Two patients were seizure free after MSI changed ICEEG from bilateral to unilateral, reducing risk. Where MSI led to ICEEG rather than no further evaluation or VNS, three patients were class I, II, and III outcome, rather than class IV, significantly improving outcome. There was no evidence of complications from MSI. In the four patients where MSI changed the decision from ICEEG to VNS, the diffuse MSI pattern predicted unlikely localization by ICEEG and VNS gave 50% to 70% seizure reduction.

An unexpected finding was that MSI spike dipole clusters occurred at a distance from the zone of seizure origin in some patients, despite MSI localization accuracy for a focal source. Most prior studies have not reported such discrepancy, but it is consistent with our previous study and not surprising.¹ The most likely explanation is recording of different spike types.³⁵ MSI information in epilepsy is indirect because it records interictal spikes. Several characteristics of interictal spikes indicate proximity to area of seizure onset.³⁶⁻³⁹ It is possible that the spikes recorded during the MSI sessions were not spikes near the zone of seizure origin. This problem could be addressed by identifying the most significant spike type by long-term EEG and then localizing it with MSI. See appendix e-6.

This study was initiated before publication of an article that used MSI dipole orientation to identify sublobar spike populations.⁴⁰ Mapping single spikes and averaged spikes yield different information. We used the same protocol over 2 years for consistency, comparison to most other centers, and proven utility.¹ We mapped clusters of single spikes to identify the spike zone population. In this study, we did not average spikes, because of inherent problems with averaged spikes³⁵ that can combine different spike foci and because to display the orientations of all single spikes usually produced a wide range of overlapping orientations and made it difficult to see the spike population clearly on the image. In the future, use of both single-spike dipoles for one image and averaged spike dipole orientation for another image may reveal more complete information.

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