Clinical Utility

Comparisons of 256-channel dEEG recordings have been made with subsampling that shows what would be seen by conventional (19-channel) EEG. These studies confirm that not only accurate *localization* but in some cases the *detection* of neuropathology may require the channel densities of 128 or 256 provided by dEEG (Holmes, 2008; Holmes et al., 2004; Lantz, et al., 2003).

Neuropathology that is limited to a small area of brain near the skull (such as a gyrus of the cortex) may project an EEG field that is invisible to conventional EEG. With the 10-20 system placement of conventional EEG, the electrodes are as far as 7 cm apart.

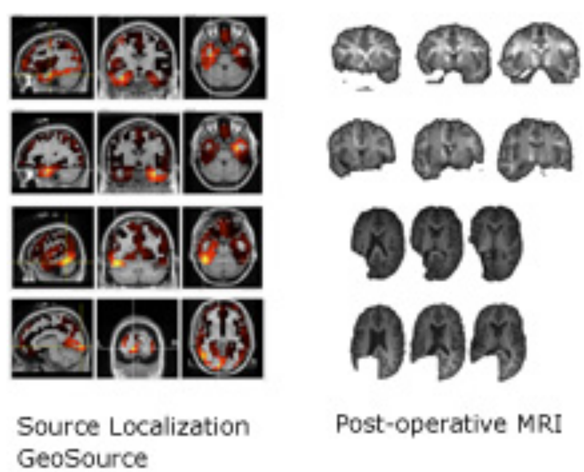
Holmes, M. D. (2008). Dense array EEG: Methodology and new hypothesis on epilepsy syndromes. *Epilepsia, 49,* 3-14.

Holmes, M. D., Brown, M., & Tucker, D. M. (2004). Are "generalized" seizures truly generalized? Evidence of localized mesial frontal and frontopolar discharges in absence. *Epilepsia, 45(12),* 1568-1579.

Lantz, G., Grave de Peralta, R., Spinelli, L., Seeck, M., & Michel, C. M. (2003). Epileptic source localization with high density EEG: how many electrodes are needed? *Clin Neurophysiol, 114(1),* 63-69.

A Review of Electrical Source Imaging

Techniques for source localization



EEG is the most central diagnostic tool for presurgical evaluation of medically intractable focal epilepsy. Typically, multichannel EEG synchronized with video monitoring is performed continuously for several days. The resulting EEG traces (or waveforms) are then analyzed for patterns typical for the patient's seizures. These patterns are assessed by the examination of the EEG traces during interictal discharges, as well as before, during, and after seizures. In the hands of an experienced epileptologist, this kind of trace analysis has a considerable value in localizing the epileptogenic area of the brain for surgery.

To obtain sufficient precision for surgery, it is important to use several complementary techniques to more accurately localize the epileptogenic foci. Modern presurgical evaluation centers generally include neurological and neuropsychological exams, high-resolution MRI, PET, and/or interictal and ictal SPECT, and sometimes MRI-based volumetry and spectroscopy in the battery of exams that aim to precisely determine the epileptogenic focus. In cases of unclear or nonconcordant results through these exams, invasive recordings from surgically implanted electrodes are usually needed as well.

Improved source-imaging algorithms greatly increase accuracy of source localization It has been argued that traditional trace analysis of the EEG only provides a fraction of the information that is available in the signal. With the advent of digitally recorded EEG, advanced analysis of the signals with modern signal processing tools is possible, allowing for much higher accuracy in focus localization. One such approach to electrical source imaging, sometimes called ESI, is the reconstruction of the electrically active areas in the brain based on the surface recordings. Since the introduction of electromagnetic source localization methods, many groups have demonstrated the usefulness of source imaging for localizing the epileptic foci based on EEG or MEG data (Binnie and Stefan, 1999; Ebersole, 1997, 2000b; Fuchs, Wagner, Köhler, and Wischmann, 1999; Hämäläinen, Hari, Ilmoniemi, Knuutila, and Lounesmaa, 1993; Mosher, Baillet, and Leahy, 1999; Patt et al., 2000). Electrical source imaging has dramatically advanced in recent years. Different source localization algorithms have been used, both dipole localization methods (Boon et al., 2000; Ebersole, 2000a, 2000b; Krings, Chiappa, Cuffin, Buchbinder, and Cosgrove, 1998; Lantz, Ryding, Holub, and Rosén, 1996; Lantz, Ryding, and Rosén, 1997; Merlet et al., 1998; Merlet and Gotman, 1999; Nayak et al., 2004; Oliva et al., 2010; Plummer, Litewka, Farish, Harvey, and Cook, 2007; Plummer, Wagner, Fuchs, Harvey, and Cook, 2010), and distributed inverse solution techniques (Fuchs et al., 1999; Huppertz, Hoegg et al., 2001; Lantz, Grave de Peralta, Gonzalez, and Michel, 2001; Lantz, Michel et al., 1997; Michel et al., 1999; Plummer, Wagner, Fuchs, Harvey et al., 2010; Plummer, Wagner, Fuchs, Vogrin et al., 2010; Seri et al., 1998; Waberski et al., 2000; Zumsteg, Friedman, Wennberg, and Wieser, 2005; Zumsteg, Friedman, Wieser, and Wennberg, 2006). These studies, which were normally performed using a standard clinical electrode setup with up to 30 electrodes, have confirmed that inverse solutions can provide an adequate definition of the epileptogenic zone. In addition, some recent studies have demonstrated the usefulness of simultaneous recording of EEG and fMRI (with subsequent source imaging of the epileptiform activity in EEG) for localizing the epileptic focus (Groening et al., 2009; Siniatchkin et al., 2010; Vulliemoz, Rodionov et al., 2010; Vulliemoz et al., 2009).

Accuracy is improved still further by upgrading to dense array EEG Even though it has been demonstrated that correct source localization results can be obtained with as few as 30 electrodes in certain simple situations, a more dense sampling of the spatial frequencies of the scalp electric fields leads to a better resolution of the topographic features. This has also been demonstrated, in simulations as well as in real data, and these studies indicate that inter-electrode distances of around 2-3 cm (corresponding to at least 100 electrodes on an adult head) are needed to avoid distortions of the scalp potential distribution (A Gevins, 1990; Spitzer, Cohen, Fabrikant, and Hallett, 1989; Srinivasan, Nunez, Tucker, Silberstein, and Cadusch, 1996; Srinivasan, Tucker, and Murias, 1998). More recent investigations, assuming a different relative conductivity between skull and brain, suggest that even higher channel counts are necessary to adequately sample brain electric fields (Gonçalves, et al, 2003; Gonçalves et al., 2003; Lai et al., 2005; Ryynänen, Hyttinen, and Malmivuo, 2004;Ryynänen, Hyttinen, and Malmivuo, 2006) In a more clinically oriented study (Lantz, et al., 2003), it was demonstrated that the localization accuracy of interictal epileptiform activity significantly improves when increasing from 32 to 64 recording channels. Increasing from 64 to 128 channels further improved the localization precision, but less significantly. This study has recently been repeated using a more accurate head model (Finite Difference Model), and with more realistic values for brain/skull conductivity differences (Lantz et al, 2009). The results of this study indicate that improvement in localization accuracy will occur up to at least 256 electrodes. This number of electrodes has previously been difficult to reach in normal clinical practice due to the considerable work of gluing the electrodes to the patient's scalp. Magnetoencephalographic (MEG) recordings are easier in this respect, since whole head systems with more than 100 sensors are available. Therefore, several groups have proposed to include whole head MEG recordings as a tool in presurgical epilepsy evaluation either alone (Baumgartner, et al., 2000; Paetau et al., 1992; Stefan et al., 2000; Wheless et al., 1999) or in combination with EEG source imaging (Ebersole and Ebersole, 2010; Tanaka et al., 2010; Wennberg, Valiante, and Cheyne, 2011). However, since the difference between EEG and MEG in localization precision is probably negligible if the same number of channels is recorded (Anogianakis et al., 1992; Cohen et al., 1990; Malmivuo, Suihko, and Eskola, 1997), it is technically, as well as economically, more practical to use the new high-resolution EEG systems, which allow the application of 128- to 256-EEG electrodes in less than 10 minutes. Several studies with 64 channel (Herrendorf et al., 2000; Huppertz, Hof et al., 2001; Waberski et al., 2000; Wang, Worrell, Yang, Wilke, and He,

2010) or 128- and 256-channel EEG systems (Brodbeck, Lascano, Spinelli, Seeck, and Michel, 2009; Brodbeck et al., 2010; Lantz, Grave de Peralta et al., 2003; Lantz, Spinelli et al., 2003; Michel, Lantz et al., 2004; Sperli et al., 2006), demonstrate the high spatial precision of epileptic focus localization that can be reached with these techniques.

Dense array EEG can also be used to localize ictal patterns Source imaging of ictal patterns is a complicated task. Only a few studies have been published using surface EEG to quantitatively localize ictal foci. In two related studies, using dipole modelling on 25-channel ictal data, Assaf and Ebersole (1997) were able to demonstrate a clear relationship between dipole orientations and intracranial ictal onset in temporal lobe patients (Assaf and Ebersole, 1997), as well as between dipole orientations and postoperative outcome in the same patient category (Assaf and Ebersole, 1999). In these two ictal studies individual waves in the time domain EEG were used for the source-imaging analysis. More quantitative approaches, such as principle component analysis (Stern et al., 2009), full-scalp frequency analysis (Blanke et al., 2000; Lantz et al., 1999; Lee et al., 2009; Michel et al., 1999) or temporal segmentation (Lantz, Michel et al., 2001) have also been used in combination with different source-imaging algorithms. In all the aforementioned studies, a standard clinical electrode setup with 20-30 electrodes was used. In another study using 64 channels (Koessler et al., 2010), the surface ictal patterns were compared to stereroelectroencephalography (SEEG), and a high level of agreement between EEG source localizations and the SEEG was obtained. Recently, the group of Holmes et al. has presented source-imaging results for epileptic seizures recorded with 128 or 256 channels. It has been demonstrated (Holmes, Brown and Tucker, 2004; Holmes, Quiring and Tucker, 2009) that so-called primary generalized seizures, such as absence seizures or seizures in juvenile myoclonic epilepsy, are not truly "generalized," with immediate global cortical involvement, but rather involve selective cortical networks including frontal and temporal regions. The same group also used high density EEG to capture seizures during clinical long term monitoring (LTM) investigations in more than 40 patients with pharmaco-resistant epilepsy, and in some cases confirmed the localization results with intracranial recordings (Holmes, 2008; Holmes et al., 2008; Holmes et al., 2010), thus demonstrating the usefulness of this technique for these purposes. **Techniques for defining functionally important brain areas** The presurgical workup and the planning of a resection of the epileptogenic zone not only involves the precise localization of the area which generates the seizures, but also areas whose resection is likely to result in an unacceptable neurological deficit. The most important areas in this respect are those involved in hand motor, visual, and language functions. Although deficits related to damage in these areas can generally be avoided based on anatomical considerations (Blume, 1993; Falconer, 1971; Lesser, Arroyo, Crone, and Gordon, 1998; Ojemann et al., 1993), many patients end up with major deficiencies, and more direct methods of defining functional relevant areas in the individual brain are needed.   The most used technique in presurgical workups for defining essential areas in individual patients is electrical cortical stimulation (ECS) complemented with intracranial evoked potentials (EPs). ECS may be carried out by stimulation in the operating room (Ojemann et al, 1989; Ojemann et al., 1993; Penfield and Jasper, 1954), or by the use of chronically implanted subdural electrodes (Lesser et al., 1998; Lesser et al., 1987). Functional MRI is a promising technique because of its high spatial resolution in individual subjects, and studies using fMRI to delineate motor areas in surgical candidates have already been presented (Nimsky et al., 1999; Schulder et al., 1999). However, for more complex functions, such as language, fMRI usually shows activation of many different parts of the brain, and the particular relevance of the different areas is not easy to determine.   High density EEG recordings combined with source localizations represent an alternative for mapping human brain functions. Because of the high temporal resolution of EEG, the activity can be followed in real time and attentional, perceptual, cognitive, and motor functions can be separated because they are likely to appear at slightly different moments in time after stimulus presentation. In this way, electromagnetic source imaging of the signals recorded during sensory, cognitive and motor tasks allows to unravel the temporal dynamics of cognitive networks without having to rely on subtraction techniques (Gevins, et al., 1999). The high spatial precision of these techniques, at least concerning the sensorimotor cortex, has been demonstrated in several studies (Ganslandt et al., 1999; Ganslandt et al., 1997; Morioka et al., 1998; Morioka et al., 1995; Rezai et al., 1997). For a more comprehensive description of the subject, see Michel et al (2004), Plummer, Harvey and Cook (2008), Barkley (2004), Baumgartner (2004) and Vulliemoz et al (2010).

Review articles

Barkley, G.L. (2004). Controversies in neurophysiology: MEG is superior to EEG in localization of interictal epileptiform activity: Pro*. Clinical Neurophysiology, 115,* 1001-1009.

Baumgartner, C. (2004). Controversies in clinical neurophysiology. MEG is superior to EEG in the localization of interictal epileptiform activity. Con. *Clinical Neurophysiology 2004, 115,* 1010-1020.

Michel, C.M., Murray, M., Lantz, G., Gonzalez, S., Spinelli, L., Grave de Peralta, R. (2004). EEG source imaging. *Clinical Neurophysiology, 115,* 2195-2222.

Plummer, C., Harvey, A.S., Cook M. (2008). EEG source localization in focal epilepsy: where are we now? *Epilepsia, 49,* 201-218.

Vulliemoz, S., Lemieux, L., Daunizeau, J., Michel, C.M., Duncan, J.S. (2010a) The combination of EEG source imaging and EEG-correlated functional MRI to map epileptic networks. *Epilepsia, 51,* 491-505.

Complete Reference List

Anogianakis, G., Badier, J. M., Barrett, G., Erné, S., Fenici, R., Fenwick, P., et al. (1992). A consensus statement of relative merits of EEG and MEG. *Electroencephalography and Clinical Neurophysiology (Editorial), 82,* 317-319.

Assaf, B. A., and Ebersole, J. S. (1997). Continuous source imaging of scalp ictal rhythms in temporal lobe epilepsy. *Epilepsia, 38,* 1114-1123.

Assaf, B. A., and Ebersole, J. S. (1999). Visual and quantitative ictal EEG predictors of outcome after temporal lobectomy. *Epilepsia, 40,* 52-61.

Barkley, G. L. (2004). Controversies in neurophysiology. MEG is superior to EEG in localization of interictal epileptiform activity: *Pro. Clinical Neurophysiology, 115(5),* 1001-1009.

Baumgartner, C. (2004). Controversies in clinical neurophysiology. MEG is superior to EEG in the localization of interictal epileptiform activity: *Con. Clinical Neurophysiology, 115(5)*, 1010-1020.

Baumgartner, C., Pataraia, E., Lindinger, G., and Deecke, L. (2000). Magnetoencephalography in focal epilepsy. *Epilepsia, 41 Suppl,* S39-S47.

Binnie, C. D., and Stefan, H. (1999). Modern electroencephalography: its role in epilepsy management. *Clinical Neurophysiology 110,* 1671-1697.

Blanke, O., Lantz, G., Seeck, M., Spinelli, L., Grave de Peralta, R., Thut, G., et al. (2000). Temporal and spatial determination of EEG-seizure onset in the frequency domain. *Clinical Neurophysiology 111,* 763-772.

Blume, W. T. (1993). Occipital lobe epilepsies. In H. O. Lueders (Ed.), *Epilepsy surgery.* (pp. 167-171). New York: Raven Press.

Boon, P., D'Have, M., Van Hoey, G., Vanrumste, B., Vonck, K., Adam, C., et al. (2000). Interictal and ictal source localization in neocortical versus medial temporal lobe epilepsy. Advances in *Neurology, 84,* 365-375.

Brodbeck, V., Lascano, A. M., Spinelli, L., Seeck, M., and Michel, C. M. (2009). Accuracy of EEG source imaging of epileptic spikes in patients with large brain lesions. *Clinical Neurophysiology, 120,* 679-685.

Brodbeck, V., Spinelli, L., Lascano, A. M., Pollo, C., Schaller, K., Vargas, M. I., et al. (2010). Electrical source imaging for presurgical focus localization in epilepsy patients with normal MRI. *Epilepsia, 51(4),* 583-591.

Cohen, D., Cuffin, B. N., Yunokuchi, K., Maniewski, R., Purcell, C., Rees Cosgrove, G., et al. (1990). MEG versus EEG localization test using implanted sources in the human brain. *Annals of Neurology, 28,* 811-817.

Ebersole, J. S. (1997). Defining epileptogenic foci: Past Present Future. Journal of Clinical *Neurophysiology, 14,* 470-483.

Ebersole, J. S. (2000a). Noninvasive localization of epileptogenic foci by EEG source modeling. *Epilepsia, 41*(suppl 3), 24-33.

Ebersole, J. S. (2000b). Sublobar localization of temporal neocortical epileptogenic foci by source modeling. *Advances in Neurology, 84,* 353-363.

Ebersole, J. S., and Ebersole, S. M. (2010). Combining MEG and EEG source modeling in epilepsy evaluations. *Journal of Clinical Neurophysiology, 27*(6), 360-371.

Falconer, M. (1971). Anterior temporal lobectomy for epilepsy. In V. Logu (Ed.), *Neurosurgery (pp. 142-149)*.London: Butterworths.

Fuchs, M., Wagner, M., Köhler, T., and Wischmann, H.-A. (1999). Linear and nonlinear current density reconstructions. *Journal of Clinical Neurophysiology, 16,* 267-295.

Ganslandt, O., Fahlbusch, R., Nimsky, C., Kober, H., Moller, M., Steinmeier, R., et al. (1999). Functional neuronavigation with magnetoencephalography: outcome in 50 patients with lesions around the motor cortex. *Journal of Neurosurgery, 91,* 73-79.

Ganslandt, O., Steinmeier, R., Kober, H., Vieth, J., Kassubek, J., Romstock, J., et al. (1997). Magnetic source imaging combined with image-guided frameless stereotaxy: a new method in surgery around the motor strip. *Neurosurgery, 41,* 621-627.

Gevins, A. (1990). Distributed neuroelectric patterns of human neocortex during simple cognitive tasks. *Progress in Brain Research, 85,* 337-345.

Gevins, A., Smith, M. E., McEvoy, L. K., Leong, H., and Le, J. (1999). Electroencephalographic imaging of higher brain function. *Philosophical Transactions of the Royal Society of London. Series B, 354,* 1125-1133.

Gonçalves, S., de Munck, J. C., Verbunt, J. P., Heethaar, R. M., and da Silva, F. H. (2003). In vivo measurement of the brain and skull resistivities using an EIT-based method and the combined analysis of SEF/SEP data. *IEEE Transactions on Biomedical Engineering, 50*(9), 1124-1128.

Gonçalves, S. I., de Munck, J. C., Verbunt, J. P., Bijma, F., Heethaar, R. M., and Lopes da Silva, F. (2003). In vivo measurement of the brain and skull resistivities using an EIT-based method and realistic models for the head. *IEEE Transactions on Biomedical Engineering, 50*(6),754-767.

Groening, K., Brodbeck, V., Moeller, F., Wolff, S., van Baalen, A., Michel, C. M., et al. (2009). Combination of EEG-fMRI and EEG source analysis improves interpretation of spike-associated activation networks in paediatric pharmacoresistant focal epilepsies. *Neuroimage, 46*(3), 827-833.

Hämäläinen, M., Hari, R., Ilmoniemi, R. J., Knuutila, J., and Lounesmaa, O. V. (1993). Magnetoencephalography—theory, instrumentation, and applications to noninvasive studies of the working human brain. *Rev. Mod. Phys., 65,* 413-497.

Herrendorf, G., Steinhoff, B. J., Kolle, R., Baudewig, J., Waberski, T. D., Buchner, H., et al. (2000). Dipole-source analysis in a realistic head model in patients with focal epilepsy. *Epilepsia 41*(1), 71-80.

Holmes, M. D. (2008). Dense array EEG: methodology and new hypothesis on epilepsy syndromes. *Epilepsia, 49* Suppl 3, 3-14.

Holmes, M. D., Brown, M., and Tucker, D. M. (2004). Are "generalized" seizures truly generalized? Evidence of localized mesial frontal and frontopolar discharges in absence. *Epilepsia, 45,* 1568-1579.

Holmes, M. D., Brown, M., Tucker, D. M., Saneto, R. P., Miller, K. J., Wig, G. S., et al. (2008). Localization of extratemporal seizure with noninvasive dense-array EEG. Comparison with intracranial recordings. *Pediatric Neurosurgery, 44,* 474-479.

Holmes, M. D., Quiring, J., and Tucker, D. M. (2009). Evidence that juvenile myoclonic epilepsy is a disorder of frontotemporal corticothalamic networks. *Neuroimage, 49*(1), 80-93.

Holmes, M. D., Tucker, D. M., Quiring, J. M., Hakimian, S., Miller, J. W., and Ojemann, J. G. (2010). Comparing noninvasive dense array and intracranial electroencephalography for localization of seizures. *Neurosurgery, 66*(2),354-362.

Huppertz, H. J., Hoegg, S., Sick, C., Lucking, C. H., Zentner, J., Schulze Bonhage, A., et al. (2001). Cortical current density reconstruction of interictal epileptiform activity in temporal lobe epilepsy. *Clinical Neurophysiology, 112*(9),1761-1772.

Huppertz, H. J., Hof, E., Klisch, J., Wagner, M., Lucking, C. H., and Kristeva-Feige, R. (2001). Localization of interictal delta and epileptiform EEG activity associated with focal epileptogenic brain lesions. *Neuroimage, 13*(1), 15-28.

Koessler, L., Benar, C., Maillard, L., Badier, J. M., Vignal, J. P., Bartolomei, F., et al. (2010). Source localization of ictal epileptic activity investigated by high resolution EEG and validated by SEEG. *Neuroimage, 51*(2),642-653.

Krings, T., Chiappa, K. H., Cuffin, B. N., Buchbinder, B. R., and Cosgrove, G. R. (1998). Accuracy of electroencephalographic dipole localization of epileptiform activities associated with focal brain lesions. *Annals of Neurology, 44*(1), 76-86.

Lai, Y., van Drongelen, W., Ding, L., Hecox, K. E., Towle, V. L., Frim, D. M., et al. (2005). Estimation of in vivo human brain-to-skull conductivity ratio from simultaneous extra- and intra-cranial electrical potential recordings. *Clinical Neurophysiology, 116*(2)*,* 456-465.

Lantz G, Brodbeck V, Seeck M, Tucker DM, Michel, CM.Electric source imaging – Increasing the number of electrodes to 256 improves source localization precision of Interictal epileptiform activity. . *Epilepsia, 2009. 50*(s11): p. 163.

Lantz, G., Grave de Peralta, R., Gonzalez, S., and Michel, C. M. (2001). Noninvasive localization of electromagnetic epileptic activity. II. Demonstration of sublobar accuracy in patients with simultaneous surface and depth recordings. *Brain Topography, 14,* 139-147.

Lantz, G., Grave de Peralta, R., Spinelli, L., Seeck, M., and Michel, C. M. (2003). Epileptic source localization with high density EEG: how many electrodes are needed? Clinical *Neurophysiology, 114*(1), 63-69.

Lantz, G., Michel, C. M., Pasqual-Marqui, R., Spinelli, L., Seeck, M., Seri, S., et al. (1997). Extracranial localisation of intracranial interictal epileptiform activity using LORETA (Low Resolution Electromagnetic Tomography). *Electroencephalography and Clinical Neurophysiology, 102,* 414-422.

Lantz, G., Michel, C. M., Seeck, M., Blanke, O., Landis, T., and Rosén, I. (1999). Frequency domain EEG source localization of ictal epileptiform activity in patients with partial complex epilepsy of temporal lobe origin. *Electroencephalography and Clinical Neurophysiology, 110,* 176-184.

Lantz, G., Michel, C. M., Seeck, M., Blanke, O., Thut, G., Landis, T., et al. (2001). Space oriented segmentation and 3-dimensional source reconstruction of ictal EEG patterns. *Clinical Neurophysiology, 112,* 687-696.

Lantz, G., Ryding, E., Holub, M., and Rosén, I. (1996). Simultaneous intracranial and extracranial recording of interictal epilptiform activity in patients with drug resistant partial epilepsy - patterns of conduction and results from dipole reconstruction. *Electroencephalography and Clinical Neurophysiology, 99,* 69-78.

Lantz, G., Ryding, E., and Rosén, I. (1997). Dipole reconstruction as a method for identifying patients with mesolimbic epilepsy. *Seizure, 6,* 303 - 310.

Lantz, G., Spinelli, L., Seeck, M., Grave de Peralta Menendez, R., Sottas, C. C., and Michel, C. M. (2003). Propagation of interictal epileptiform activity can lead to erroneous source localizations: A 128 channel EEG mapping study. *Journal of Clinical Neurophysiology, 20*(5)*,* 311-319.

Lee, E. M., Shon, Y. M., Jung, K. Y., Lee, S. A., Yum, M. K., Lee, K. n., et al. (2009). Low resolution electromagnetic tomography analysis of ictal EEG patterns in mesial temporal lobe epilepsy with hippocampal sclerosis. *Clinical Neurophysiology 120*(10), 1797-1805.

Lesser, R. P., Arroyo, S., Crone, N., and Gordon, B. (1998). Motor and sensory mapping of the frontal and occipital lobes. *Epilepsia, 39*(Suppl.4)*,* S69-S80.

Lesser, R. P., Lueders, H. O., Klem, G., Dinner, D. S., Morris, H. H., Hahn, J.

F., et al. (1987). Extraoperative cortical functional localization in patients with epilepsy. *Journal of Clinical Neurophysiology, 4,* 27-53.

Malmivuo, J., Suihko, V., and Eskola, H. (1997). Sensitivity distributions of EEG and MEG measurements. *IEEE Transactions on Biomedical Engineering, 44,* 196-208.

Merlet, I., Garcia-Larrea, L., Ryvlin, P., Isnard, J., Sindou, M., and Mauguière, F. (1998). Topographical reliability of mesio-temporal sources of interictal spikes in temporal lobe epilepsy. *Electroencephalography and Clinical Neurophysiology, 107,* 206-212.

Merlet, I., and Gotman, J. (1999). Reliability of dipole models of epileptic spikes. *Clinical Neurophysiology, 110,* 1013-1028.

Michel, C. M., Grave de Peralta, R., Lantz, G., Gonzalez Andino, S., Spinelli, L., Blanke, O., et al. (1999). Spatio-temporal EEG analysis and distributed source estimation in presurgical epilepsy evaluation. *Journal of Clinical Neurophysiology, 16,* 225-238.

Michel, C. M., Lantz, G., Spinelli, L., Grave de Peralta Menedez, R., Landis, T., and Seeck, M. (2004). 128-channel EEG source imaging in epilepsy: clinical yield and localization precision. *Journal of Clinical Neurophysiology, 21*(2)*,* 71-83.

Michel, C. M., Murray, M., Lantz, G., Gonzalez, S., Spinelli, L., and Grave de Peralta, R. (2004). EEG source imaging. *Clinical Neurophysiology, 115*(10)*,* 2195-2222.

Morioka, T., Shigeto, H., Ishibashi, H., Nishio, S., Yamamoto, T., Yoshiura, T., et al. (1998). Magnetic source imaging of the sensory cortex on the surface anatomy MR scanning. *Neurological Research, 20,* 235-241.

Morioka, T., Yamamoto, T., Mizushima, A., Tombimatsu, S., Shigeto, H., Hasuo, K., et al. (1995). Comparison of magnetoencephalography, functional MRI, and motor evoked potentials in the localization of the sensory-motor cortex. *Neurological Research, 17,* 361-367.

Mosher, J. C., Baillet, S., and Leahy, R. M. (1999). EEG source localization and imaging using multiple signal classification approaches. *Journal of Clinical Neurophysiology, 16,* 225-238.

Nayak, D., Valentin, A., Alarcon, G., Seoane, J. J. G., Brunnhuber, F., Juler, J., et al. (2004). Characteristics of scalp electrical fields associated with deep medial temporal epileptiform discharges. *Clinical Neurophysiology, 115,* 1423-1435.

Nimsky, C., Ganslandt, O., Kober, H., Moller, M., Ulmer, S., Tomandl, B., et al. (1999). Integration of functional magnetic resonance imaging supported by magnetoencephalography in functional neuronavigation. *Neurosurgery, 44,* 1249-1255.

Ojemann, G. A., Ojemann, J., Lettich, E., and Berger, M. (1989). Cortical language localization in left, dominant hemisphere. *Journal of Neuosurgery, 71,* 316-326.

Ojemann, G. A., Sutherling, W. W., Lesser, R. P., Dinner, D. S., Jayakar, P., and Saint-Hilaire, J. M. (1993). Cortical stimulation. In J. Engel (Ed.), *Surgical Treatment of the Epilepsies*. New York: Raven Press.

Oliva, M., Meckes-Ferber, S., Roten, A., Desmond, P., Hicks, R. J., and O'Brien, T. J. (2010). EEG dipole source localization of interictal spikes in non-lesional TLE with and without hippocampal sclerosis. *Epilepsy Research, 92*(2-3), 183-190.

Paetau, R., Kajola, M., Karhu, J., Nousiainen, U., Partanen, J., Tiihonen, J., et al. (1992). Magnetoencephalographic localization of epileptic cortex--impact on surgical treatment. *Annals of Neurology, 32,* 106-109.

Patt, S., Steenbeck, J., Hochstetter, A., Kraft, R., Huonker, R., Haueisen, J., et al. (2000). Source localization and possible causes of interictal epileptic activity in tumor-associated epilepsy. *Neurobiology of Disease, 7,* 260-269.

Penfield, W. J., and Jasper, H. H. (1954). *Epilepsy and the functional anatomy of the human brain*. Boston: Little Brown and Co.

Plummer, C., Harvey, A. S., and Cook, M. (2008). EEG source localization in focal epilepsy: where are we now? *Epilepsia, 49(2),* 201-218.

Plummer, C., Litewka, L., Farish, S., Harvey, A. S., and Cook, M. J. (2007). Clinical utility of current-generation dipole modelling of scalp EEG. *Clinical Neurophysiology, 118*(11),2344-2361.

Plummer, C., Wagner, M., Fuchs, M., Harvey, A. S., and Cook, M. J. (2010). Dipole versus distributed EEG source localization for single versus averaged spikes in focal epilepsy. *Journal of Clinical Neurophysiology, 27*(3), 141-162.

Plummer, C., Wagner, M., Fuchs, M., Vogrin, S., Litewka, L., Farish, S., et al.

(2010). Clinical utility of distributed source modelling of interictal scalp EEG in focal epilepsy. *Clinical Neurophysiology, 121*(10), 1726-1739.

Rezai, A. R., Mogilner, A. Y., Cappell, J., Hund, M., Llinas, R. R., and Kelly, P. J. (1997). Integration of functional brain mapping in image-guided neurosurgery. *Acta Neurochirurgica, 68* (Suppl), 85-89.

Ryynänen, O., Hyttinen, J., and Malmivuo, J. (2004). Study on the spatial resolution of EEG--effect of electrode density and measurement noise. *Conference Proceedings - IEEE Engineering in Medicine and Biology Society, 6,* 4409-4412.

Ryynänen, O. R., Hyttinen, J. A., and Malmivuo, J. A. (2006). Effect of measurement noise and electrode density on the spatial resolution of cortical potential distribution with different resistivity values for the skull. *IEEE Transactions on Biomedical Engineering, 53*(9), 1851-1858.

Schulder, M., Holodny, A., Liu, W. C., Gray, A., Lange, G., and Carmel, P. W. (1999). Functional magnetic resonance image-guided surgery of tumors in or near the primary visual cortex. *Stereotactic and Functional Neurosurgery, 73,* 31-36.

Seri, S., Cerquiglini, A., Pisani, F., Michel, C. M., Pascual Marqui, R. D., and Curatolo, P. (1998). Frontal lobe epilepsy associated with tuberous sclerosis: electroencephalographic-magnetic resonance image fusioning. *Journal of Child Neurology, 13,* 33-38.

Siniatchkin, M., Groening, K., Moehring, J., Moeller, F., Boor, R., Brodbeck, V., et al. (2010). Neuronal networks in children with continuous spikes and waves during slow sleep. *Brain, 133*(9), 2798-2813.

Sperli, F., Spinelli, L., Seeck, M., Kurian, M., Michel, C. M., and Lantz, G. (2006). EEG source imaging in pediatric epilepsy surgery: a new perspective in presurgical workup. *Epilepsia, 47*(6), 981-990.

Spitzer, A. R., Cohen, L. G., Fabrikant, J., and Hallett, M. (1989). A method for determining optimal interelectrode spacing for cerebral topographic mapping. *Electroencephalography and Clinical Neurophysiology, 72,* 355-361.

Srinivasan, R., Nunez, P. L., Tucker, D. M., Silberstein, R. B., and Cadusch, P. J. (1996). Spatial sampling and filtering of EEG with spline laplacians to estimate cortical potentials. *Brain Topography, 8,* 355-366.

Srinivasan, R., Tucker, D. M., and Murias, M. (1998). Estimating the spatial

Nyquist of the human EEG. *Behavior Research Methods, Instruments and Computers, 30,* 8-19.

Stefan, H., Hummel, C., Hopfengartner, R., Pauli, E., Tilz, C., Ganslandt, O., et al. (2000). Magnetoencephalography in extratemporal epilepsy. *Journal of Clinical Neurophysiology, 17*(2),190-200.

Stern, Y., Neufeld, M. Y., Kipervasser, S., Zilberstein, A., Fried, I., Teicher, M., et al. (2009). Source localization of temporal lobe epilepsy using PCA-LORETA analysis on ictal EEG recordings. *Journal of Clinical Neurophysiology, 26,* 109-116.

Tanaka, N., Hämäläinen, M. S., Ahlfors, S. P., Liu, H., Madsen, J. R., Bourgeois, B. F., et al. (2010). Propagation of epileptic spikes reconstructed from spatiotemporal magnetoencephalographic and electroencephalographic source analysis. *Neuroimage, 50*(1), 217-222.

Tucker, D. M. (1993). Spatial sampling of head electrical fields: the geodesic sensor net. *Electroencephalography and Clinical Neurophysiology, 87,* 154-163.

Vulliemoz, S., Lemieux, L., Daunizeau, J., Michel, C. M., and Duncan, J. S. (2010). The combination of EEG source imaging and EEG-correlated functional MRI to map epileptic networks. *Epilepsia, 51*(4)*,* 491-505.

Vulliemoz, S., Rodionov, R., Carmichael, D. W., Thornton, R., Guye, M., Lhatoo, S. D., et al. (2010). Continuous EEG source imaging enhances analysis of EEG-fMRI in focal epilepsy. *Neuroimage, 49*(4), 3219-3229.

Vulliemoz, S., Thornton, R., Rodionov, R., Carmichael, D. W., Guye, M., Lhatoo, S., et al. (2009). The spatio-temporal mapping of epileptic networks: combination of EEG-fMRI and EEG source imaging. *Neuroimage, 46*(3), 834-843.

Waberski, T. D., Gobbelé, R., Herrendorf, G., Steinhoff, B. J., Kolle, R., Fuchs, M., et al. (2000). Source reconstruction of mesial temporal epileptiform activity: comparison of inverse techniques. *Epilepsia, 41,* 1574-1583.

Wang, G., Worrell, G., Yang, L., Wilke, C., and He, B. (2010). Interictal spike analysis of high-density EEG in patients with partial epilepsy. *Clinical Neurophysiology,* in press.

Wennberg, R., Valiante, T., and Cheyne, D. (2011). EEG and MEG in mesial temporal lobe epilepsy: Where do the spikes really come from? *Clinical Neurophysiology,* e-pub ahead of print.

Wheless, J. W., Willmore, L. J., Breier, J. I., Kataki, M., Smith, J. R., King, D. W., et al. (1999). A comparison of magnetoencephalography, MRI, and V-EEG in patients evaluated for epilepsy surgery. *Epilepsia, 40,* 931-941.

Zumsteg, D., Friedman, A., Wennberg, R. A., and Wieser, H. G. (2005). Source localization of mesial temporal interictal epileptiform discharges: correlation with intracranial foramen ovale electrode recordings. *Clinical Neurophysiology, 116*(12), 2810-2818.

Zumsteg, D., Friedman, A., Wieser, H. G., and Wennberg, R. A. (2006). Propagation of interictal discharges in temporal lobe epilepsy: correlation of spatiotemporal mapping with intracranial foramen ovale electrode recordings. . *Clinical Neurophysiology, 117,* 2615-2626.