NONINVASIVE SOURCE LOCALIZATION
OF EXTENDED CORTICAL SOURCES:
Electroencephalographic and Magnetoencephalographic Source Imaging
of Human K-complexes and Temporal Lobe Spikes

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ABSTRACT

Electroencephalographic source imaging (ESI) and magnetoencephalographic source imaging (MSI) are used to identify brain regions responsible for generating the electromagnetic fields recorded outside the head using electroencephalography (EEG) and magnetoencephalography (MEG). However, as applied to the extended cortical sources underlying the high amplitude EEG and MEG potentials characteristic of human sleep and epilepsy, few studies have directly examined: (a) the reliability of ESI and MSI techniques and (b) the physiologic validity of ESI and MSI localization. This thesis examines the validity and reliability of current generation ESI and MSI as applied to these extended cortical sources.

In a first study the intracranial localization of the largest potential in the normal human EEG, the sleep K-complex, was determined using stereoelectroencephalography (simultaneous scalp and intracranial EEG). The cortical field thus identified was chosen for further study as representative of a large superficial bilateral extended source.

In a second study the intracranial localizations of interictal spike foci in patients with temporal lobe epilepsy were determined using stereoelectroencephalography. The anterolateral temporal neocortical field of the classical anterior temporal spike focus was chosen for further study as representative of a smaller, unilateral extended source.

In a third study ESI and MSI were used to model the K-complex, and results compared to the true intracranial source. Results were reliable in terms of consistency from one K-complex to the next, however, solutions were falsely localized deep to the superficial cortical source. Distributed source modeling was not better than dipole mapping in this regard.
In a fourth and fifth study ESI and MSI were used to model the anterior temporal spike field, and results compared to the true intracranial source. Reliability of ESI performed on single spikes was low, but valid localizations were consistently achieved with ESI performed on averages of topographically identical spikes. This was true for both dipole mapping and distributed source modeling. MSI localizational validity showed an expected dependence on source orientation and a similar improvement in reliability when performed on averaged spikes. Minimization of physiologic noise through signal averaging is important to maximize reliability and validity when modeling extended cortical sources of this size.
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LIST OF ABBREVIATIONS

BEM = boundary element method
bid = twice daily
CE = confidence ellipsoid
cm = centimetres
CT = computerized tomography
ECOG = electrocorticography
EEG = electroencephalography
EPSP = excitatory post-synaptic potential
ESI = EEG (electrical) source imaging
FCD = fixed coherent dipole
FEMi = leadfield-interpolated finite element method
fT = femtotesla
HFF = high frequency filter
Hz = hertz
ICA = independent component analysis
IPSP = inhibitory post-synaptic potential
LFF = low frequency filter
m = meters
MEG = magnetoencephalography
MSI = MEG (magnetic) source imaging
MGFP = mean global field power
mm = millimetres
MRI = magnetic resonance imaging
MNI = Montreal Neurological Institute
MNLS = minimum norm least squares
ms = milliseconds
MTLE = mesial temporal lobe epilepsy
mV = millivolts
nA = nanoamperes
PCA = principle component analysis
qhs = once a day, at bedtime
sLORETA = standardized low-resolution electromagnetic tomography
SNR = signal to noise ratio
T = tesla
tid = three times a day
µV = microvolts
V = volts
$V'$ = explained variance
Chapter One

Introduction
INTRODUCTION

Electroencephalographic source imaging (ESI) and magnetoencephalographic source imaging (MSI) are used increasingly in clinical and research settings to identify areas of the human brain responsible for generating the electromagnetic fields recorded outside the head using electroencephalography (EEG) and magnetoencephalography (MEG). However, as applied to the extended cortical sources responsible for generation of the spontaneous high amplitude EEG and MEG potentials characteristic of human sleep and epilepsy, only rare studies have attempted to directly examine: (a) the reliability of ESI and MSI techniques and (b) the physiologic validity of EEG and MEG source localizations. This thesis examines the validity and reliability of current generation ESI and MSI techniques as applied to these extended cortical sources.

For clinical purposes, ESI and MSI methods have been most commonly used to aid in demarcation of interictal spike foci during presurgical investigations of patients with medically intractable epilepsy (Ebersole, 1997; Knowlton et al., 1997, 2006; Mamelak et al., 2002; Patarazza et al., 2002; Fischer et al., 2005; Plummer et al., 2007, 2008; Agirre-Arzizubieta et al., 2009; Brodbeck et al., 2011).

For research purposes, ESI and MSI methods have been applied to the high amplitude spontaneous potentials characteristic of non-REM sleep and idiopathic (primary) generalized epilepsy, with the aim of better understanding the mechanisms underlying these normal and abnormal neurophysiological processes (Rodin et al., 1994; Holmes et al., 2004, 2010; Tucker et al., 2007; Murphy et al., 2009).

With respect to noninvasive source localization of interictal spikes, for ESI and MSI to be routinely recommended it must be demonstrated that the techniques are both reliable (i.e., that identical spikes generated in a particular brain region are associated with consistently localized source solutions) and physiologically valid (i.e., that the source solution of an interictal spike accurately represents the true intracranial cortical generator of the extracranially-recorded spike).
In addition, it is important that new clinical techniques such as ESI and MSI can be
demonstrated to have true added value. To the clinical neurophysiologist, it is of little benefit to
perform additional, complex and time consuming tests if the final localization results are no better
than what can be obtained from a quick visual analysis of the data.

With respect to potential research applications of ESI and MSI in the study of sleep and
generalized epilepsy, it will be necessary to show that noninvasive source modeling can provide
physiologically valid results before ESI and MSI can be accepted as useful techniques for
research in these areas.

The gold standard and only currently available way to accurately assess the validity of a
noninvasive source solution is through direct comparison with the intracranially recorded
electrical field (Merlet and Gotman, 1999; Gavaret et al., 2004; Zumsteg et al., 2005; Plummer et
al., 2007, 2008). Investigations of this sort have been performed infrequently in clinical studies of
interictal spikes in focal epilepsy, either by comparing intracranially recorded spike fields with
previous noninvasive ESI or MSI results (Sutherling et al., 1988; Nakasato et al., 1994; Ko et al.,
1998; Merlet and Gotman, 1999; Leitjen et al., 2003; Bast et al., 2004; Gavaret et al., 2004, 2006,
2009; Agirre-Arrizubieta et al., 2009; Huiskamp et al., 2010) or, rarely, by comparing ESI or MSI
solutions with simultaneously acquired intracranial EEG spike fields (Lantz et al., 1996, 2001;
Mikuni et al., 1997; Oishi et al., 2002; Shigeto et al., 2002; Yamazaki et al., 2012).

Noninvasive source modeling results obtained in research studies of sleep slow waves
and generalized spike and wave complexes have supported (patho)physiologic interpretations of
subcortical generation and thalamocortical network function (Rodin et al., 1994; Holmes et al.,
2004, 2010; Tucker et al., 2007; Murphy et al., 2009), however, these results have not been
validated against intracranial electrical field recordings.

Methodological issues regarding intracranial localization of electrical fields associated with
extracranial EEG/MEG waveforms
Synchronous neuronal activity in extended sources involving at least 6 cm² of cortex, and often more than 10-20 cm², underlies the spontaneous electromagnetic potentials visible above the background activity in EEG or MEG (Cooper et al., 1965; Tao et al., 2007). These potentials represent the effects of summed excitatory post-synaptic potentials (EPSPs) or summed inhibitory post-synaptic potentials (IPSPs) acting on pyramidal cells in superficial cortex, as described by the classical dipole layer model (Gloor, 1985). In line with the dipole layer model, surface negative potentials are associated with a volume conducted intracranial electrical field that is inverted in polarity (with respect to the surface negative extended cortical source), and which appears with zero time-delay at disparate intracranial electrode contacts, including those situated within subcortical white matter. This synchronous intracranial electropositive field represents the “opposite”, positive side of the extended surface negative cortical dipole layer (Gloor, 1985; Wennberg, 2010a; Appendix 1).

Interpretation of volume conducted intracranial fields as recorded by depth electrode contacts can be complicated and is dependent not only on the size of the source generator (Zaveri et al., 2009; Wennberg, 2010a; Appendix 1) but also on the montages (bipolar or referential) used to depict the electrical fields (Wennberg and Lozano, 2006). Analyses of simultaneously recorded intracranial and extracranial fields, combined with understanding and application of the dipole layer model, can facilitate interpretations regarding the localization and orientation of extended cortical sources (Wennberg et al., 2002; Wennberg and Lozano, 2003).

Fig. 1.1 shows a rare, historical, intracranial recording obtained from a single 5-contact depth electrode in a young patient during a generalized absence seizure. The 3 Hz spike and wave activity is depicted in the intracranial recording in a bipolar montage, and the EEG localizational concept of “phase reversal” was used in the original paper to suggest that the spike and wave activity was generated in the thalamus (Williams, 1953; Fig. 1.1). Thalamic generation of spike and wave activity in primary generalized epilepsy was a prevailing concept at the time, and the intracranial EEG results were interpreted to provide support for that concept (Williams, 1953).
However, viewed in hindsight, a more parsimonious interpretation of the same recording would suggest that the intracranial field is more likely compatible with an extended surface negative cortical generator and its associated, inverted (electropositive), volume conducted subcortical field (see Fig. 1.1 legend for further detail). The inability at the time to digitally reformat the same potentials from bipolar to referential montages made historical interpretation a more difficult enterprise than it is today. Notwithstanding, enough information is present in the bipolar recording – if the extracranial and intracranial fields are envisaged within the neurophysiological constraint of the dipole layer model – to infer that the electrical fields are most compatible with a surface negative superficial cortical source localization.

Fig. 1.2 provides a modern example, using digital reformatting, of the differences in appearance of the same intracranial spike field (in this case, a temporal lobe spike in an adult patient with focal epilepsy) when viewed in a bipolar versus a referential montage. One can see that localization by “phase reversal” of the intracranial field in the bipolar montage would falsely place the source generator deep to the true superficial cortical source, similar to the localization presented in Fig. 1.1. Reformatting the intracranial recording to a monopolar referential montage makes clear the correct interpretation of a surface negative superficial cortical localization (see Fig. 1.2 legend for further detail).

Selection of K-complexes and anterior temporal spikes as objects of study

The K-complex was chosen as an object of study for this thesis because it is the highest amplitude spontaneous potential in the human EEG, and thus likely an ideal candidate to represent very large, bilaterally synchronous extended cortical sources. A signature element of sleep, new information derived about the cortical localization of the K-complex, and the ability to model its cortical generators noninvasively, would be important to advance our understanding of the neurophysiology of human sleep. The K-complex was also chosen for study because its cortical localization is likely to mirror that of the generalized spike and wave complex of primary
generalized epilepsy. Primary (idiopathic) generalized epilepsy is a common condition neither needing nor amenable to surgical intervention; as such, apart from rare instances (e.g., Williams, 1953), intracranial EEG recordings are not available to validate the results of noninvasive source localization studies. However, experimental and clinical evidence suggests that the neuroanatomical and neurophysiological network circuitry involved in K-complex and spike and wave complex formation share common features (Gloor, 1968; Snead III, 1995), and that K-complexes may even be precursors to spike and wave complexes (Amzica and Steriade, 2002).

Fig. 1.3 shows examples of spike and wave complexes and K-complexes recorded in a patient with primary generalized epilepsy, and highlights the topographic similarities of the extracranially recorded EEG voltage fields. It is probable that information revealed through intracranial EEG and source modeling studies of the K-complex would also be relevant to the spike and wave complex.

The anterior temporal spike of mesial temporal lobe epilepsy (MTLE) was chosen as an object of study because (a) it is to date the most investigated spontaneous potential in the field of clinical noninvasive source imaging, (b) it represents a smaller, unilateral extended source, providing a contrast to the larger, bilateral K-complex, and (c) it is of accepted diagnostic importance but, at the same time, controversial with respect to its cortical localization and pathophysiologic significance. Fig. 1.4 shows bilateral independent spikes recorded with simultaneous extracranial and intracranial EEG in a patient with MTLE. Focal intracranial spikes limited to the hippocampus in the mesial temporal region are not visible in the scalp EEG; on the other hand, scalp visible spikes are associated with large, inverted volume conducted spike fields (Fig. 1.4). Whether or not spikes generated within the mesial temporal structures can be recorded extracranially with EEG and MEG, and whether or not diagnostic anterior temporal spikes in MTLE can be accurately modeled using ESI or MSI, have been subjects of debate for more than two decades (Ebersole and Wade, 1990; Ebersole, 1997, 2000; Boon et al., 1997; Lantz et al., 1997; Merlet et al., 1998; Shindo et al., 1998; Merlet and Gotman, 1999; Baumgartner et al.,
2000; Waberski et al., 2000; Huppertz et al., 2001; Lantz et al., 2001; Shigeto et al., 2002; Gavaret et al., 2004; Michel et al., 2004a; Kobayashi et al., 2005; Stephen et al., 2005; Zumsteg et al., 2005; Plummer et al., 2007, 2008; Agirre-Arrizubieta et al., 2009; Kaiboriboon et al., 2010). Definitive resolution of these enduring contentious issues will be important for the advancement of ESI and MSI in epilepsy.

In a general sense, direct validation of ESI and MSI results against data derived from intracranial EEG recordings is important to ensure that (patho)physiological interpretations are truly supported by the noninvasive source modeling results, whether the object of investigation is a part of normal or abnormal human neurophysiology. There may be a temptation in source localization studies to rely on established neuroanatomical and neurophysiological conceptions to uncritically accept ESI and MSI findings. The studies that make up this thesis avoid such temptation by directly comparing – against their intracranial electrical fields – the electromagnetic source imaging results obtained in modeling the K-complexes of sleep, and the temporal lobe spikes of epilepsy.
Fig. 1.1. Recording of an absence seizure in a 9 year old. Single 5-contact depth electrode, 2 cm between contacts, contact 1 deepest. Ventriculography indicated contact 1 in ventrolateral thalamus, contact 2 near postero-ventrolateral nucleus, just above pulvinar, contact 3 in subcortical white matter, contact 4 near deep surface of cortex, contact 5 just inside scalp. EEG channel is a bipolar recording between frontal and parietal scalp electrodes. Electronegativity is depicted as upward deflection in this adaptation of original tracing. Bipolar intracranial recordings demonstrate a region of electropositive near equipotentiality between contacts 2 and 3 (slightly more positive at contact 3 than contact 2). Though interpreted in the original to indicate generation of the generalized spike and wave discharge in the thalamus (at contact 2), the subcortical electropositive electrical fields are compatible with generation of the visible surface negative spike and wave discharges in superficial cortex. The different bipolar depth electrode channels show the field at the most superficial contact 5 to be more negative than at contact 4 (recording from deeper cortex), the field at contact 4 to be more negative than at contact 3 (recording from white matter, the electrode contact at this site “seeing” the opposite, electropositive side of the cortical dipole layer, the difference between negativity at contact 4 and positivity at contact 3 accentuating algebraically the amplitude of the waveforms in this channel), the field at contact 3 to be slightly more positive than at contact 2, and the field at contact 2 to be more positive than at contact 1, representing the fall off in amplitude of the volume conducted electropositive field seen intracranially in subcortical structures at increased distance from the cortical generating surface. (Adapted from Figs. 2, 3 and 4 in Williams, 1953; used with permission, Oxford University Press).
**Fig. 1.2.** Left temporal focal spike and wave discharge in an adult patient with temporal lobe epilepsy. Spike component of epileptiform discharge shown at fast sweep speed. Single 4-contact depth electrode, 1 cm between contacts, deepest contact in the hippocampus, most superficial contact within lateral temporal neocortex. EEG channel (above horizontal line) is a monopolar referential recording at scalp electrode T3; reference electrode = Pz (same potential depicted to left and right of depth electrode), negative up. Bipolar intracranial recording demonstrates a region of electropositive equipotentiality between the second and third contacts of the depth electrode (slightly more positive at the spike peak at the third (more superficial) than second (deeper) contact). Digital reformatting of the intracranial recording of the same epileptiform discharge to a monopolar referential montage (reference = scalp electrode Pz) shows that the polarity of the electrical field reverses at the level of the temporal neocortex (electronegative extracranially and electropositive intracranially in the subcortical white matter and distant hippocampus). There is an increasing amplitude decay of the volume conducted electropositive field evident at the three deepest contacts, the amplitude falling off with increased distance from the superficial cortical generating source. The most superficial depth electrode contact, situated deep within the large neocortical area responsible for generation of the scalp-recorded EEG spike, “sees” a combination of local electronegative and electropositive fields associated with the cortical spike source, in this case showing a slight predominance of the deeper cortical layer electropositive fields.
Figure 1.3

(A) Absence seizure (3 Hz generalized spike and wave) in an adult patient with primary generalized epilepsy. Bilaterally synchronous spike and wave discharges are of maximal amplitude over the midline frontal region. (B) Three K-complexes recorded during stage 2 sleep in the same patient; the second K-complex is associated with an intermingled single generalized spike and wave discharge. (C) Average of 7 generalized spike and wave discharges (left) and average of 7 K-complexes (right) recorded in same patient. Surface voltage topographic plots of the spike (bottom left) and wave (bottom middle) components of the generalized spike and wave discharge, and the K-complex peak (bottom right). The spike, wave and K-complex peaks have nearly identical topographic distributions. Common average (12 scalp electrodes) referential montage; LFF = 0.5 Hz; HFF = 70 Hz.
Figure 1.4

Fig. 1.4. Comparison of intracranial temporal lobe interictal epileptiform discharges recorded during sleep with simultaneous scalp EEG. Focal spikes in left and right hippocampi (LH spike, electrode contact LDH1, and RH spike, electrode contact RDH1, respectively) show no scalp EEG correlates. More diffuse right temporal spike and wave complexes (RT EEG spike) apparent at multiple contacts of right temporal depth electrode (RDH1-4) are associated with visible epileptiform potentials on scalp EEG (F8, T4). Referential montage; reference = common average 10-20 electrodes. Top 16 channels = scalp EEG. Channels 17-20 and 21-24 = left and right, respectively, temporal depth electrode recordings; 4-contact orthogonally implanted depth electrodes, deepest contact of each electrode in the hippocampus, most superficial contact in deep surface of lateral temporal neocortex. Sensitivity = 15 μV/mm for scalp EEG, 50 μV/mm for intracranial recordings. (Adapted from Fig. 2.9 in Wennberg, 2011; used with permission, CRC Press).
Chapter Two

Aims and hypotheses
AIMS AND HYPOTHESES

The overall aim of this research was to examine the reliability and validity of electromagnetic source imaging, as applied to the extended cortical sources responsible for generation of EEG and MEG potentials characteristic of human sleep and epilepsy. The experimental design involved a series of separate studies, each with a specific aim.

Study 1. A study using stereoelectroencephalography (simultaneous scalp and intracranial EEG) aiming to determine the location and extent of the cortical source underlying the human K-complex. The discovery of this information would be used later to study the validity of noninvasive source modeling applied to this large, extended cortical source.

Study 2. A study using stereoelectroencephalography aiming to delineate the location and extent of cortical sources underlying interictal epileptiform discharges (spikes) in mesial temporal lobe epilepsy. This information would be used later to study the validity of noninvasive source modeling applied to these smaller, unilateral cortical sources.

Study 3. A study examining the reliability and validity of electromagnetic source imaging applied to the K-complex, using the information discovered in Study 1 as a gold standard. Specific hypotheses included: (a) that dipole source solutions for the extended superficial cortical field would be falsely mislocalized deep, interhemispherically, because of the nature of the dipole modeling algorithm; and (b) that distributed source modeling algorithms would provide more realistic, accurate source localization.

Studies 4 and 5. Two studies, using EEG and MEG, respectively, examining the reliability and validity of electromagnetic source imaging applied to classical anterior temporal lobe spikes. The
intracranial cortical source localization information determined in Study 2 served as a gold standard for these two studies. Specific hypotheses included: (a) that mesial temporal dipole source solutions for extracranially recorded EEG and MEG spikes represent deep mislocalizations, because temporolimbic spikes are not detectable in unaveraged extracranial EEG or MEG; (b) that scattered dipole sources do not represent extended regions of epileptogenic cortex but rather limitations in reliability of the source imaging techniques, given the similarity of extracranial spike appearance and large area of synchronously active cortex needed to generate the potentials; and (c) that distributed source modeling would provide more realistic source localization.
Chapter Three

Literature Review
Intracranial cortical localization of extended cortical sources

The K-complex

The K-complex was identified in the human EEG more than 70 years ago and is a basic component of the neurophysiology of sleep (Loomis et al., 1938; Colrain, 2005). It is the highest amplitude graphic element in the normal EEG, and its principal components consist of a large surface-negative slow sharp wave followed by a positive slow wave peaking 300-400 ms after the major negative peak (Loomis et al., 1938; Roth et al., 1956; Colrain, 2005). Much has been learned about the cellular mechanisms underlying K-complex formation and much written regarding the putative function of K-complexes in the regulation of sleep and arousal (Amzica and Steriade, 2002; Colrain, 2005). Nevertheless, the localization of the intracranial generators of the K-complex in the human brain is an unresolved issue (Cote et al., 1999; Colrain, 2005).

Results from animal and human studies have shown that K-complexes are generated in the cortex, as opposed to subcortical structures (Amzica and Steriade, 1998, 2002; Wennberg and Lozano, 2003; Colrain, 2005), and the midline frontal scalp EEG maximum of K-complexes certainly suggests a bilateral anterior hemispheric predominance (Davis et al., 1939; Brazier, 1949; Roth et al., 1956; Colrain et al., 1999; Cote et al., 1999; Colrain, 2005). More detailed knowledge of the intracranial distribution of the human K-complex, however, is not available (Brazier, 1949; Cote et al., 1999; Colrain, 2005). Is the K-complex distributed widely and synchronously over the lateral anterior cortices? Or are the mesial interhemispheric cortices involved preferentially – or not at all? Are the limbic structures of the brain involved? These questions have not been answered. A small number of published reports attempting to localize the site of K-complex generation using dipole mapping of scalp EEG or MEG have provided conflicting and sometimes implausible results (Ueno and Iramina, 1990; Lu et al., 1992; Iramina and Ueno, 1996; Numminen et al., 1996), with different papers suggesting sources in the centrotemporal area (Ueno and Iramina, 1990; Iramina and Ueno, 1996), inferior parietal region (Lu et al., 1992), or frontal and parietal regions (Numminen et al., 1996).
In a recent paper investigating the neurophysiology of K-complexes, Cash et al. (2009) interpreted intracranial macroelectrode recordings as evidence that human K-complexes have a widespread intracortical generation. Combined with simultaneously acquired microelectrode recordings, the authors concluded that K-complexes represent widespread cortical down-states, potentially important for sleep maintenance and memory consolidation (Cash et al., 2009).

The microelectrode recordings presented in (Cash et al., 2009) indicate with certainty intracortical generation of K-complexes in the lateral frontal, superior temporal and temporoparietal areas that were sampled. However, the intracranial field depicted in the averaged macroelectrode recordings (Fig. 1B in Cash et al., 2009) is incompatible with the classically recognized predominance of the K-complex over the midline frontal region. A high amplitude negative field in the EEG maximal over the frontal region cannot be generated intracranially by (i) a surface-negative field in the occipital, parietal, inferior temporal and orbitofrontal cortices and (ii) a simultaneous surface-positive field in the prefrontal cortex (as depicted in Fig. 1B in Cash et al., 2009). Such an intracranial field would of necessity produce in the scalp EEG a posterior and inferior cranial negativity and an anterior frontal positivity.

Cash et al. (2009) argued that recording K-complexes from macroelectrodes on the cortical surface was highly likely to indicate local intracortical generation near the electrode contact. However, depending on the amplitude and extent of the field, local generation is not necessarily likely. Specifically, in the case of K-complexes, representation in the deep, posterior and inferior aspects of the brain may be entirely due to volume conduction from a distant anterior and superior electrical field (Wennberg, 2010a). Microelectrode recordings in the posterior and inferior brain surfaces could resolve this with certainty, but study of the intracranial fields is enough to show that human K-complexes are not generated across all cortical lobes.

It is difficult to ascertain how the K-complex distribution reported in (Cash et al., 2009) was arrived at. Inadvertant polarity inversion of some tracings could be responsible, but no single inversion could explain all of the incorrect polarities. Reference electrode contamination is
another possibility, and very little information was provided about this technical aspect of the macroelectrode recordings, only that intradural electrodes facing away from the cortex were used as references (Cash et al., 2009). No information was given as to where these electrodes were situated or to what extent they may have acted as active electrodes. One could envision reference electrode contaminations that might explain certain of the incorrect waveforms in Fig. 1 of (Cash et al., 2009), e.g., frontopolar positivity might result from an active superior frontal reference, whereby greater negativity at the reference electrode site would produce relative positivity at the more anterior frontopolar site, despite true surface negativity at the latter site. However, no single reference electrode position could explain all of the incorrect waveform polarities in (Cash et al., 2009).

Another possibility is that the very few (one to four) scalp electrodes used in (Cash et al., 2009) may have been insufficient to accurately identify K-complexes, especially if no electrodes were placed over the frontal regions. This may have led to false identification of some non-K-complex slow waves as K-complexes.

Temporal lobe spikes in mesial temporal lobe epilepsy

There has been much debate as to whether or not interictal epileptiform activity (spikes) generated within the mesial temporal structures can be recorded extracranially with EEG and MEG, and this issue is particularly relevant for source localization studies (Ebersole and Wade, 1990; Ebersole, 1997, 2000; Boon et al., 1997; Lantz et al., 1997; Merlet et al., 1998; Shindo et al., 1998; Merlet and Gotman, 1999; Baumgartner et al., 2000; Waberski et al., 2000; Huppertz et al., 2001; Lantz et al., 2001; Shigeto et al., 2002; Gavaret et al., 2004; Michel et al., 2004a; Kobayashi et al., 2005; Stephen et al., 2005; Zumsteg et al., 2005; Plummer et al., 2007, 2008; Agirre-Arrizubieta et al., 2009; Kaiboriboon et al., 2010).

For more than 50 years intracranial EEG recordings, initially using intraoperative electrocorticography (ECOG) and later supplemented with chronic intracranial EEG, have
demonstrated that patients with MTLE have spikes generated independently from multiple regions of one or both temporal lobes. The intracranial spike fields have been shown to range in size from less than 1 cm² (e.g., apparent at only one contact in a row of adjacent intracranial electrodes) to more than 20 cm², with independent spikes recorded from the limbic structures of the mesial temporal region and from the anterior and/or basal and/or lateral temporal lobe neocortices (Talairach and Bancaud, 1966; Niedermeyer and Rocca, 1972; Gloor, 1975; Privitera et al., 1990; Marks et al., 1992; Quesney and Niedermeyer, 1993; Tsai et al., 1993; Wennberg et al., 1997a; Fernández Torre et al., 1999; Gavaret et al., 2004; Tao et al., 2007; Goncharova et al., 2009). It has been reported that waveforms visible with (unaveraged) scalp EEG require synchronous neuronal activity extending across at least 6 cm² of cortex (Cooper et al., 1965), and that typical temporal spikes reflect activity in large neocortical areas 10-20 cm² in size, and never activity limited to mesial structures (Merlet and Gotman, 1999; Gavaret et al., 2004; Zumsteg et al., 2006a; Tao et al., 2007). Intraoperative ECOG and chronic intracranial EEG have demonstrated that high amplitude spikes restricted to one or more of the limbic structures in the mesial temporal region are not detected by intracranial electrode contacts situated over the lateral temporal neocortex, let alone by scalp EEG (Tsai et al., 1993; Alarcon et al., 1994; Wennberg et al., 1997a,b; Gavaret et al., 2004; Zumsteg et al., 2006a), such that one might reasonably question a priori whether noninvasive recordings could ever be expected to detect mesial temporal spikes. Nayak et al. (2004) found that only 9% of all temporal lobe spikes detected intracranially by foramen ovale electrodes were visible on scalp EEG without averaging. Similar reservations pertain to MEG, which is thought to be even less sensitive to deep sources than EEG (Mikuni et al., 1997; Baumgartner et al., 2000; Oishi et al., 2002; Rampp and Stefan, 2007). Shigeto et al. (2002) showed that mesial temporal spikes recorded by intracranial EEG were not detected by simultaneous MEG.

Many investigations have provided empirical or theoretical evidence that spikes restricted to the mesial temporal structures are not detected with EEG or MEG (Alarcon et al., 1994;
Mikuni et al., 1997; Merlet and Gotman, 1999; Baumgartner et al., 2000; Oishi et al., 2002; Shigeto et al., 2002; Gavaret et al., 2004; Nayak et al., 2004; Zumsteg et al., 2006a; Tao et al., 2007). Alarcon et al. (1994), based on empirical data, calculated a current dipole strength on the order of 2 nA·m for a typical intracranially recorded hippocampal spike, which would produce a volume conducted scalp peak voltage of 0.45 µV (and an 88 fT peak MEG field), far too small to be detected above the baseline background activity. Assuming the same estimate of current density, a 100µV temporal lobe scalp EEG spike would require a mesial temporal focal dipole strength of approximately 100-600 nA·m – equivalent to an 80 mV hippocampal spike, approximately two orders of magnitude greater in amplitude than any spike recorded in the human brain (Alarcon et al., 1994). Dipole modeling results localizing EEG or MEG spikes to the mesial temporal region have calculated hypothetical hippocampal dipole strengths of 300-600 nA·m, which are not compatible with a highly focal source in the hippocampus, and do not correspond to the empirical data derived from intracranial EEG (Alarcon et al., 1994). Similarly, simulation studies have estimated that current densities must be on the order of 10-100 nA·m/mm² to create a measurable extracranial EEG or MEG field, which are up to two orders of magnitude higher than typical values cited in the literature (Alarcon et al., 1994; Stephen et al., 2005).

Nevertheless, source localization algorithms applied to visible EEG or MEG spikes showing mesial temporal solutions have been interpreted to indicate that the extracranially visible spikes may be generated within the deep mesial temporal structures (Boon et al., 1997; Lantz et al., 1997; Merlet et al., 1998; Plummer et al., 2007, 2008; Kaiboriboon et al., 2010), something that appears at odds with simple visual analysis of the intracranial fields associated with extracranial EEG and MEG spike fields in MTLE.

Mesial temporal spikes identified by intracranial EEG can be averaged (on the intracranial potential) to produce volume conducted low amplitude far fields measurable in simultaneously acquired scalp EEG recordings, and the sources of these averaged far field
potentials can be accurately modeled to the mesial temporal regions (Nayak et al., 2004; Zumsteg et al., 2005). However, the individual mesial temporal spikes in these studies were dependent on intracranial EEG for detection.

Propagation of temporal lobe spikes has been frequently described and mesial limbic to lateral neocortical propagation is often inferred to underlie the generation of spikes recorded with EEG and MEG in MTLE (Baumgartner et al., 1995; Ebersole et al., 1995; Ebner and Hoppe, 1995; Fuchs et al., 1999; Merlet and Gotman, 1999; Scherg et al., 1999; Lantz et al., 2003; Pataraia et al., 2005; Zumsteg et al., 2006b; Ebersole and Hawes-Ebersole, 2007; Kobayashi et al., 2009; Kaiboriboon et al., 2010). However, studies using different intracranial EEG recording arrays have described independence of mesial limbic and lateral neocortical temporal lobe spikes (Alarcon et al., 1994, 1997; Wennberg et al., 1997a,b; Merlet and Gotman, 1999; Gavaret et al., 2004). A lack of dependency on hippocampal drive for the generation of neocortical spikes in MTLE is not surprising if one considers the longstanding observation that typical temporal neocortical spikes are not necessarily abolished (and may in fact become more abundant) after selective surgical resection of the ipsilateral mesial temporal structures (Niemeyer, 1958; Cendes et al., 1993; Wennberg et al., 1997b).

**Noninvasive source imaging of extended cortical sources**

Noninvasive source localization, or source imaging, holds promise for determining the particular region(s) of the brain responsible for generating the waveforms recorded outside the skull with EEG or MEG. The idea that one may accurately solve this “inverse problem” of neurophysiology, formulated by Helmholtz more than 150 years ago (Helmholtz, 1853), may at first appear fanciful, as the inverse problem does not have a unique solution. In other words, the problem is considered by definition to be ill-posed. Nevertheless, empirical evidence accumulated over recent decades has enabled many advances in source imaging techniques, and the ability to constrain inverse solutions to only those that are physiologically plausible has increased the face
validity of results. In the field of epilepsy, where accurate determination of the brain region(s) responsible for generation of epileptiform activity is vital for the surgical treatment of patients, it has been proposed that noninvasive source imaging using EEG and MEG has now advanced to the point that it may be ready to play a role in routine clinical investigation (Knowlton et al., 1997, 2006; Otsubo et al., 2001; Fischer et al., 2005; Paulini et al., 2007; Plummer et al., 2007, 2008; Rampp and Stefan, 2007; Agirre-Arrizubieta et al., 2009; Brodbeck et al., 2011).

*K*-complexes, *sleep slow waves, generalized spike and wave complexes*

The application of EEG and MEG source imaging to the human K-complex has produced conflicting and occasionally implausible results (Ueno and Iramina, 1990; Lu et al., 1992; Iramina and Ueno, 1996; Numminen et al., 1996; Colrain, 2005).

The burgeoning research interest in sleep neurophysiology is certain to be accompanied by increasing attempts to incorporate noninvasive EEG and MEG source localization techniques to study various aspects of the K-complex, and it will be important to resolve whether or not these techniques are able to accurately depict the brain areas involved in K-complex generation.

The surface negative peak of the K-complex (sometimes referred to as the N550) is the highest amplitude potential in the normal human EEG (Loomis et al., 1938; Roth et al., 1956; Colrain, 2005). Paradoxically, at the cellular level, it is associated with a widespread cortical down-state characterized by suppression of neuronal activity (Amzica and Steriade, 2002; Cash et al., 2009; Cserca et al., 2010; Dalal et al., 2010; Le Van Quyen et al., 2010). In line with the cortical dipole layer model (Gloor, 1985), the surface negative peak of the K-complex must represent the effects of either: (a) summated excitatory post-synaptic potential (EPSP) inputs to the superficial apical dendrites of frontal lobe cortical pyramidal cells, or (b) summated inhibitory post-synaptic potential (IPSP) inputs at the deeper cell soma level of these same pyramidal cells. The bulk of the available evidence obtained from animal and human microelectrode recordings supports the second option: i.e., that synchronized hyperpolarizing IPSPs synapsing on pyramidal
cell bodies in deeper layers of the cortical mantle are primarily responsible for initiation of the principal negative wave of the K-complex (Cash et al., 2009; Cserca et al., 2010; Dalal et al., 2010; Le Van Quyen et al., 2010).

The localization of the presumptive inhibitory inputs is unknown; however, it is reasonable to implicate the thalamus (and possibly other subcortical structures) given the known involvement of reciprocal thalamocortical circuits in slow oscillatory sleep patterns (Amzica and Steriade, 1998, 2002; Steriade and Amzica, 1998). The paucity of cortical neuronal activity during the K-complex down-state suggests that cortical contributions to the inhibitory inputs may be less likely.

The extent and timing of synchronization during the negative K-complex peak is also incompletely understood. Does cortical synchronization arise from synchrony of the subcortical hyperpolarizing IPSPs synapsing simultaneously on the soma of the relevant frontal lobe cortical pyramidal cells? Or, once initiated in one cortical region, does the K-complex propagate across the cortex, either through synaptic transmission similar to sleep slow wave propagation (Amzica and Steriade, 1995) or perhaps even as a result of endogenous electric field activity (Fröhlich and McCormick, 2010)? If synaptic propagation occurs, would it originate at the inhibitory input neurons (e.g., within the thalamus) or would it arise from corticocortical connectivity? It has been hypothesized, based on high density scalp EEG recordings and noninvasive source localization, that sleep slow waves and K-complexes may represent traveling waves propagating across the cortical surface, usually from front to back, guided along a deep interhemispheric “cingulate highway” (Massimini et al., 2004; Murphy et al., 2009), although this hypothesis has not been verified using intracranial EEG.

Recent fMRI studies have correlated K-complexes with positive blood oxygen level-dependent (BOLD) signal changes in subcortical (brainstem and thalamus) and cortical regions, the latter involving mainly paracentral, posterior and inferior parieto-occipital, superior temporal, and midline cingulate and paracingulate structures (Caporro et al., 2012; Jahnke et al., 2012). It is
of interest to note that the areas of BOLD changes outline regions of the brain that an
electroencephalographer would presume would not be implicated in generation of the negative
wave of the K-complex. It is conceivable that the subcortical BOLD changes might reflect the
source(s) of the inhibitory neuronal activity acting upon cortical pyramidal cell bodies to produce
the negative wave of the K-complex. However, the other (predominantly posterior and inferior)
cortical areas of BOLD changes may be more likely representative of increased neuronal activity
during the subsequent up-state associated with the later, lower amplitude, positive wave of the K-
complex (the temporal resolution of fMRI being insufficient to identify neuronal activity confined
to any single wave component of the K-complex; Jahnke et al., 2012).

Previous reports describing EEG or MEG source localization of the K-complex using
dipole mapping or, in one case, distributed source modeling, presented various source solutions in
deep centrotemporal (Ueno and Iramina, 1990; Iramina and Ueno, 1996), inferior parietal (Lu et
al., 1992) or frontal and parietal areas (Numminen et al., 1996), all of which would seem to be
doubtful given the classically recognized midline frontal EEG maximum of the K-complex.

One particular problem for noninvasive source localization of high amplitude, bilaterally
synchronous potentials such as K-complexes, sleep slow waves, or generalized spike and wave
complexes, is the inherent tendency of inverse models to provide deep interhemispheric solutions
for large, bilaterally synchronous cortical sources (Nunez, 1990; Romani and Pizzella, 1990;
Hämäläinen et al., 1993; Numminen et al., 1996; Colrain, 2005; Kobayashi et al., 2005; Zumsteg
and Wennberg, 2005). This may be especially relevant to source localization using single
equivalent current dipole models, although it is unclear whether cortically-constrained distributed
source models will necessarily perform better (Zumsteg and Wennberg, 2005).

Reliability and validity of source imaging in epilepsy

Technological advances in recent years have made noninvasive source imaging methods
more widely available to end users and ESI and MSI are likely to be used increasingly in the
clinical investigation of patients with epilepsy (Knowlton et al., 1997, 2006; Otsubo et al., 2001; Fischer et al., 2005; Paulini et al., 2007; Plummer et al., 2007, 2008; Rampp and Stefan, 2007; Agirre-Arrizubieta et al., 2009; Brodbeck et al., 2011).

**Partial (focal) epilepsy, temporal lobe spikes, EEG**

There has been surprisingly little research published that addresses the issues of reliability and validity of ESI in the clinical setting. Clinical ESI studies in epilepsy have concentrated primarily on temporal lobe epilepsy and have usually addressed reliability and validity only indirectly (Michel et al., 2004a; Plummer et al., 2008; Brodbeck et al., 2011). Validity has been most commonly assessed by looking for correlations between source localization solutions and surgical outcomes. In the most typical example, spikes localized to the temporal lobe by ESI were presumed to be valid if a patient became seizure free after surgical resection of the anteromesial temporal lobe (Waberski et al., 2000; Huppertz et al., 2001; Michel et al., 2004b; Brodbeck et al., 2011; Wang et al., 2011). However, particularly for MTLE, seizure freedom after anteromesial temporal resection does not depend on removal of the neocortical areas responsible for generation of a patient’s typical interictal spikes (Cendes et al., 1993; Wennberg et al., 1997a). Indeed, MTLE patients’ anterior temporal neocortical spikes often become more abundant after selective surgical resection of the ipsilateral mesial temporal structures responsible for seizure generation (Niemeyer, 1958; Cendes et al., 1993; Wennberg et al., 1997b). In consideration of these longstanding observations, it has been suggested that assessing the validity of temporal lobe interictal spike source localizations by correlating with surgical outcomes may not be entirely rational (Zumsteg et al., 2005; Plummer et al., 2008).

Other studies have used source localizations of interictal spikes in the vicinity of structural lesions identified by neuroimaging to presume validity of ESI data (Boon et al., 1997; Diekmann et al., 1998; Krings et al., 1998; Worrell et al., 2000; Huppertz et al., 2001; Lantz et al., 2003a; Michel et al., 1999, 2004b). However, it is well known from intracranial EEG
recordings that interictal spikes may be localized at some distance from structural lesions (Talairach and Bancaud, 1966; Zumsteg et al., 2005), such that this method of assessing validity is also less than ideal.

These sorts of analyses (correlations with surgical outcomes and structural lesions) have been interpreted to indicate that ESI has good localization accuracy at the lobar or sublobar level (Lantz et al., 1997; Shindo et al., 1998; Fuchs et al., 1999; Scherg et al., 1999; Michel et al., 1999, 2004a; Ebersole, 2000; Ebersole and Hawes-Ebersole, 2007). However, given that simple visual analysis of an EEG recording containing focal interictal spikes usually presents no problem for an electroencephalographer to presume localization of the spike generator at a lobar or sublobar level, for ESI to be of added clinical benefit it must be able to reliably provide accurate source localizations at a much finer level.

The reliability of ESI in the clinical setting has been addressed less frequently than validity (Plummer et al., 2007, 2008). The few relevant studies have compared results obtained from modeling individual versus averaged spikes, with some evidence to suggest marked improvements in reliability with spike averaging (Bast et al., 2004, 2006). Nonetheless, most ESI continues to be performed on individual spikes or averages of a small, often unspecified, number of spikes.

The gold standard and only currently available way to accurately assess the validity of an ESI solution is through direct comparison with the intracranially recorded spike field (Merlet and Gotman, 1999; Gavaret et al., 2004; Zumsteg et al., 2005; Plummer et al., 2007, 2008). Investigations of this sort have been infrequently performed, either by comparing intracranially recorded spike fields with previous noninvasive ESI (Merlet and Gotman, 1999; Gavaret et al., 2004, 2006, 2009) or, rarely, by comparing ESI solutions with simultaneously acquired intracranial EEG spike fields (Lantz et al., 1996, 2001; Yamazaki et al., 2012).
*Partial (focal) epilepsy, temporal lobe spikes, MEG*

The validity of source localization results obtained using MSI has typically been assessed by comparisons with postsurgical outcomes (Sutherling et al., 1988; Nakasato et al., 1994; Wheless et al., 1999; Iwasaki et al., 2002; Mamelak et al., 2002; Assaf et al., 2004; Bast et al., 2004; Genow et al., 2004; Fischer et al., 2005; Papinicolaou et al., 2005; Patarai et al., 2005; Knowlton et al., 2006; Oishi et al., 2006; Paulini et al., 2007; RamachandranNair et al., 2007; Kaiboriboon et al., 2010), structural lesions visible on brain MRI (Nakasato et al., 1994; Knowlton et al., 1997; Diekmann et al., 1998; Otsubo et al., 2001; Bast et al., 2004), regions of metabolic abnormalities demonstrated using other functional imaging techniques such as PET and SPECT (Stefan et al., 1992; Lamusuo et al., 1999; Sakamoto et al., 2003), localization of ictal onset zones using intracranial EEG recordings obtained later during patients’ investigations (Sutherling et al., 1988; Stefan et al., 1992; Knowlton et al., 1997; Minassian et al., 1999; Otsubo et al., 1999; Hisada et al., 2001; Mamelak et al., 2002; Assaf et al., 2004; Knowlton et al., 2006; Oishi et al., 2006) and occasionally interictal intracranial EEG findings obtained during later chronic or acute electrocorticography investigations (Sutherling et al., 1988; Nakasato et al., 1994; Ko et al., 1998; Leijten et al., 2003; Bast et al., 2004; Agirre-Arrizubieta et al., 2009; Huiskamp et al., 2010).

Most of these methods have limitations with respect to validating the source localization results obtained using MEG, including (a) the fact that the interictal spikes modeled with MSI are frequently recorded at a distance from the seizure generating regions of the brain, especially for MTLE, where seizure freedom after anteromesial temporal resection does not depend on removal of the neocortical areas responsible for generation of the extracranially recorded interictal spikes (Cendes et al., 1993; Tran et al., 1995; Wennberg et al., 1997a,b; Knowlton et al., 2006; Wennberg, 2006), (b) the longstanding observation that interictal spikes are frequently recorded at a distance from structural lesions and do not necessarily show a fine degree of overlap with hypometabolic lesions visualized with other functional imaging techniques (Talairach and
Bancaud, 1966; Sakamoto et al., 2003; Zumsteg et al., 2005; Bagshaw et al., 2006), and (c) that the comparison of interictal spikes modeled with MSI and ictal intracranial EEG recordings is a method comparing two different entities, which are in a broad sense related but not necessarily bound to overlap closely at a fine level of localization in the brain.

The reliability of the results obtained using MSI performed on identical spikes has not been a topic of systematic research. Rare simultaneous MEG and intracranial EEG recordings have concentrated primarily on determining the sensitivity of MEG to detect intracranially recorded spikes (Mikuni et al., 1997; Oishi et al., 2002; Shigeto et al., 2002), as have studies that have directly compared MSI results with interictal spikes recorded during subsequent electrocorticographic recordings (Agirre-Arrizubieta et al., 2009; Huiskamp et al., 2010). These investigations have not directly examined the degree to which MSI may provide a reliable source solution for a given spike generated from a single spike focus, i.e., the degree to which MSI may be expected to show a consistent result whenever applied to a spike that corresponds to a well-characterized focal cortical source, as confirmed by intracranial recordings in the same patient.

It has become common clinical practice to consider clusters of MEG dipole sources as a localizing marker extended in space, possibly representing the overall extent of epileptogenic cortex responsible for giving rise to similar appearing spikes recorded with MEG (Otsubo et al., 2001; Mamelak et al., 2002; Bast et al., 2004; Oishi et al., 2006; Ramachandran Nair et al., 2007). This concept has frequently enabled useful localization at the lobar level (Otsubo et al., 2001; Mamelak et al., 2002; Pataaraia et al., 2002; Stefan et al., 2003; Oishi et al., 2006; Paulini et al., 2007; Ramachandran Nair et al., 2007), however, the underlying premise that the extent of the source solution cluster represents the extent of the epileptogenic cortex comprising a spike focus in the brain has not been fully tested. The hypothesis that dipole source clusters represent an extended region of cortex capable of generating independent spikes – that appear topographically similar extracranially – is based on the concept that such spikes may be generated from anywhere within a brain region comprising many square centimeters, with no single focal maximum to the
true intracranial spike source. However, *a priori*, another equally plausible explanation for clusters of scattered dipole sources may simply be spatial inaccuracy of the noninvasive source localization methodology – spikes with the same extracranial topographic fields might actually have a consistent focal cortical source maximum that may not be reliably modeled, from one spike to the next, by existing MSI techniques (Bast et al., 2004).
Chapter Four

Intracranial cortical localization of the human K-complex

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Abstract

Objective: The K-complex was first identified in human sleep EEG more than 70 years ago, but the localization of its intracranial generators is an unresolved issue. In this study, K-complexes recorded using simultaneous scalp and intracranial EEG were analyzed to discover the intracranial distribution of the human K-complex.

Methods: Stereoelectroencephalographic recordings were performed in six patients with medically-refractory epilepsy. Full 10-20 scalp montages were used and intracranial macroelectrodes sampled medial, lateral and basal frontal and temporal cortices, medial and lateral parietal and occipital cortices, as well as the hippocampus and thalamus. Spontaneous K-complexes were visually identified in stage II sleep and averaged off-line.

Results: The intracranial K-complex field was maximal over the anterior and superior aspects of the medial and lateral frontal lobe cortices, consistent with the frontal midline scalp EEG maximum. The frontal maximum surface-negative field was volume conducted as an inverted, positive field posteriorly and inferiorly, the polarity reversing laterally above the inferior temporal region and medially above the cingulate cortex.

Conclusions: As suggested by the scalp EEG topography, the intracranial distribution of the human K-complex is maximal over the anterior and superior frontal cortices. K-complex generation appears limited to cortical regions above the inferior temporal sulcus laterally, the cingulate sulcus medially and the parietooccipital junction posteriorly.

Significance: The human K-complex is produced by synchronous cortical activity that appears maximal intracranially over the superior medial and lateral aspects of the frontal lobes. The cingulate cortex and functionally related mesial temporal structures appear uninvolved in human K-complex generation.
4.1. Introduction

The K-complex was identified in the human EEG more than 70 years ago and is a basic component of the neurophysiology of sleep (Loomis et al., 1938; Colrain, 2005). It is the highest amplitude graphic element in the normal EEG, and its principal components consist of a large surface-negative slow sharp wave followed by a positive slow wave peaking 300-400 ms after the major negative peak (Loomis et al., 1938; Roth et al., 1956; Colrain, 2005). Much has been learned about the cellular mechanisms underlying K-complex formation and much written regarding the putative function of K-complexes in the regulation of sleep and arousal (Amzica and Steriade, 2002; Colrain, 2005). Nevertheless, the localization of the intracranial generators of the K-complex in the human brain is an unresolved issue (Cote et al., 1999; Colrain, 2005).

Results from animal and human studies have shown that K-complexes are generated in the cortex, as opposed to subcortical structures (Amzica and Steriade, 1998, 2002; Wennberg and Lozano, 2003; Colrain, 2005), and the midline frontal scalp EEG maximum of K-complexes certainly suggests a bilateral anterior hemispheric predominance (Davis et al., 1939; Brazier, 1949; Roth et al., 1956; Colrain et al., 1999; Cote et al., 1999; Colrain, 2005). More detailed knowledge of the intracranial distribution of the human K-complex, however, is not available (Brazier, 1949; Cote et al., 1999; Colrain, 2005). Is the K-complex distributed widely and synchronously over the lateral anterior cortices? Or are the mesial interhemispheric cortices involved preferentially – or not at all? Are the limbic structures of the brain involved? These questions have not been answered. A small number of published reports attempting to localize the site of K-complex generation using dipole mapping of scalp EEG or MEG have provided conflicting and sometimes implausible results (Ueno and Iramina, 1990; Lu et al., 1992; Iramina and Ueno, 1996; Numminen et al., 1996), with different papers suggesting sources in the centrottemporal area (Ueno and Iramina, 1990; Iramina and Ueno, 1996), inferior parietal region (Lu et al., 1992), or frontal and parietal regions (Numminen et al., 1996).
In this study, K-complexes recorded from six patients with epilepsy undergoing simultaneous scalp and intracranial EEG monitoring were averaged and their field of distribution depicted on the mesial and lateral cortical surfaces of the hemispheres, as well as within the thalamus and subcortical white matter. The findings provide a detailed intracranial EEG picture of the cortical distribution of the human K-complex.

### 4.2. Methods

Stereoelectroencephalographic recordings using simultaneous scalp EEG and intracranial macroelectrodes were performed in six patients with medically-refractory epilepsy, either as part of their routine clinical investigation to determine candidacy for epilepsy surgery (patients 1-5), or as part of a clinical protocol following surgical implantation of deep brain stimulating electrodes for epilepsy (patient 6) (Hodaie et al., 2002; Wennberg and Lozano, 2003). All patients gave informed consent and studies were approved by the institutional research ethics board.

Recordings were carried out using a full set of scalp EEG electrodes, comprising at least 19 electrodes placed according to the International 10-20 system. Simultaneous intracranial macroelectrode recordings were obtained from stereotactically implanted 4 or 6 contact subdural strip electrodes, sometimes in combination with 4 contact depth electrodes (Ad-Tech, Racine, WI, USA) or, in the case of patient 6, from 4 contact deep brain stimulating electrodes (Medtronic, Minneapolis, MN, USA) prior to internalization of the latter for therapeutic purposes (Hodaie et al., 2002; Wennberg and Lozano, 2003). Location of the intracranial electrodes was verified by magnetic resonance imaging (MRI). The acquisition reference electrode was placed at FCz with a ground at Fpz. Recordings were obtained using a digital EEG system (XLTEK, Oakville, ON, Canada) and a sampling frequency of 200 or 500 Hz.

K-complexes were visually identified in stage 2 sleep during the first or second night of patients’ clinical recordings, using standard electrographic criteria (Rechtschaffen and Kales, 1968), and artifact-free samples archived for off-line analysis. Waveforms were averaged (35-50
per patient) to reduce background activity fluctuations using Insight software (Persyst, Prescott, AZ, USA). Individual K-complexes were averaged on the extreme value of the scalp EEG channel with maximal amplitude in referential (common average) montage at the major surface-negative peak (usually Fz, occasionally F3 or F4, rarely Fp1 or Fp2).

For all of the figures in this paper, the scalp EEG and intracranial macroelectrode recordings have been digitally reformatted and are shown in common average reference montages, the common average reference for all patients comprising the following twelve scalp electrodes: T3, T5, F3, C3, P3, O1, F4, C4, P4, O2, T4, T6. For the scalp EEG display (Fig. 4.1), this common average reference leads to a slight exaggeration of occipital positivity, related to contamination of the common average with the high amplitude negative K-complex field recorded at F3 and F4. However, this scalp common average serves as an excellent reference for the intracranial macroelectrode recordings, which are, on average, approximately five times greater in amplitude than the scalp recordings. This amplitude difference between the scalp EEG and the intracranial recordings is such that for K-complexes any scalp electrode reference will allow for relatively accurate display of the intracranial fields, however, the common average reference is used here for the added benefit of spatially averaging the scalp background activity to reduce baseline fluctuations in the reference signal. Supplementary data Fig. 4.S1 shows examples of the effects of different reference electrode selections (linked ears, O2, Sp2, FCz) upon the K-complex waveforms and demonstrates the suitability of the common average reference.

4.2.1. Subjects

Patient 1. A 30 year old man with complex partial seizures with or without secondary generalization. Antiepileptic drugs (AEDs): topiramate 200 mg bid, levetiracetam 1500 mg bid, phenytoin 100 mg bid. Left orbitofrontal seizure onsets, active (>1 spike/min) left temporal interictal spikes. Brain MRI normal. Seizure free after resection of left inferior frontal and
orbitofrontal gyri plus anterior temporal resection. Surgical pathology: no microscopic abnormalities.

*Patient 2.* A 30 year old woman with complex partial seizures with or without secondary generalization. AEDs: gabapentin 800 mg bid, phenobarbital 120 mg qhs. Left posterior temporal neocortical seizure onsets, inactive (<<1 spike/min) independent left temporal anteromesial and posterolateral interictal spikes. Brain MRI normal. Persistent seizures after left temporal neocortical resection; resection limited by involvement of receptive language cortex in epileptogenic zone. Surgical pathology: mild gliosis, cortex and white matter of superior temporal gyrus.

*Patient 3.* A 31 year old woman with simple and complex partial seizures with or without secondary generalization. AEDs: carbamazepine mg 600 tid, valproic acid mg 500 tid. Independent left posterior temporal neocortical and right mesial temporal seizure onsets, inactive (<1 spike/min) bilateral independent mesial temporal interictal spikes. Brain MRI normal. No surgical resection.

*Patient 4.* A 27 year old woman with complex partial seizures with or without secondary generalization. AEDs: levetiracetam 1000 mg bid, lamotrigine 200 mg bid. Right anterior frontal seizure onsets, inactive (<<1 spike/min) lateral and medial frontal interictal spikes. Brain MRI normal. Seizure free after right frontal lobectomy. Surgical pathology: no microscopic abnormalities.

*Patient 5.* A 27 year old man with complex partial seizures with or without secondary generalization. AEDs: carbamazepine mg 700 bid, valproic acid mg 750 mg bid. Right occipital seizure onsets, active (>>1 spike/min) right occipital interictal spikes, independent active (>1 spike/min) left and right anteromesial temporal interictal spikes. Brain MRI showed right occipital encephalomalacia due to presumed prenatal infarct. Seizure free after right occipital lobectomy plus resection of right parahippocampal gyrus and hippocampectomy. Surgical pathology: coarse occipital gliosis with extensive hemosiderin deposition, porencephalic cleft
between posterior aspect of lateral ventricle and occipital cortex, abnormal occipital gyral pattern, interpreted as sequelae of focal prenatal hemorrhagic vascular event.

**Patient 6.** A 43 year old man with complex partial seizures with or without secondary generalization. AEDs: phenytoin 200 mg bid, clobazam 10 mg bid. Left posterior temporal neocortical seizure onsets suspected on scalp EEG, rare scalp EEG midtemporal interictal spikes. Brain MRI normal. Intracranial recording not performed in this patient for determination of epilepsy surgery candidacy given presumed proximity of seizure onset zone to language cortex; treated instead with thalamic deep brain stimulation.

**4.3. Results**

The scalp EEG distributions of the averaged K-complexes recorded in each patient showed the classical frontal midline maximum negative field (Fig. 4.1).

The intracranial distribution of the K-complex is shown in Fig. 4.2 as a composite diagram composed of the averaged waveforms recorded from the mesial and lateral cortical surfaces and deep midline structures in the six patients. A summary of averaged K-complexes recorded at some of the cortical and subcortical sites most relevant for demonstrating the intracranial field distribution is presented in Fig. 4.3.

The K-complex field is maximal intracranially over the anterior and superior aspects of the medial and lateral frontal lobe cortices, consistent with the frontal midline scalp EEG maximum. The surface-negative frontal maximum intracranial field gradually diminishes posteriorly and inferiorly, reversing in polarity laterally over the inferior temporal region. Unexpectedly, the surface-negative field was found to have an earlier inferior polarity inversion mesially, occurring above the cingulate gyrus (Figs. 4.2, 4.3).

The inverted K-complex waveform polarity in the white matter of the frontal lobe (Fig. 4.3), where recording electrode contacts “see” the opposite, positive side of the surrounding surface-negative frontal dipole layer, confirms intracortical generation of the K-complex within
the frontal cortices, as opposed to generation in a deep midline or more posterior source (which would produce volume conducted frontal white matter and surface fields of the same polarity).

K-complex waveforms in the cingulate cortex, thalamus, and white and gray matter of the inferomesial temporal and occipital lobes showed a uniformly inverted, positive polarity with respect to the surface-negative, frontally predominant K-complex field (Figs. 4.2, 4.3). This distribution can only be explained by intracranial volume conduction of the large, anteriorly and superficially generated electrical field, with the positive side of the summated dipolar field recorded inferiorly and posteriorly. Thus, K-complex generation appears limited to cortical regions above the inferior temporal sulcus laterally, the cingulate sulcus medially and the parietooccipital junction posteriorly.

The locations of all implanted macroelectrodes are shown both schematically and on brain MRI for each patient in Figs. 4.4-4.9, along with the averaged waveforms recorded from each electrode site, providing a more complete illustration of the intracranial field of distribution of the human K-complex as recorded in each patient.

Analysis of averaged intracranial K-complexes afforded greater waveform clarity due to the increased signal-to-noise ratio that resulted from averaging the spontaneous background activity present in the macroelectrode recordings. However, the characteristic distributions and polarities of the intracranial K-complex field could also be appreciated in unaveraged waveforms, albeit with lesser clarity and with some variations between individual waveforms, the latter more evident at surface cortical (as opposed to subcortical) electrode sites. Examples of unaveraged K-complexes recorded in patients 1, 3 and 6 are presented in Figs. 4.10-4.12. The individual, unaveraged waveforms represent a superposition of the locally-generated and volume conducted K-complex activity and the spontaneous background activity.
4.4. Discussion

The intracranial K-complex field appears maximal and surface-negative over the anterior and superior aspects of the medial and lateral frontal lobe cortices, consistent with the frontal midline scalp-negative EEG maximum. Polarity inversion is seen in the white matter of the frontal lobe, a finding consistent with a previously published observation in a patient with psychosis (Sem-Jacobsen et al., 1953). This subcortical polarity inversion is also consistent with the classical dipole layer model presumed to underlie generation of most potentials in the EEG (Gloor, 1985): electrode contacts within the frontal white matter record the opposite, positive side of the surrounding surface-negative frontal dipole layer. Farther away, the large, anteriorly and superiorly maximal surface-negative field is volume conducted posteriorly and inferiorly in the brain as an inverted, positive field, the polarity reversing laterally above the inferior temporal region and medially above the cingulate cortex.

This intracranial field indicates that K-complexes are generated by widespread synchronous cortical activity arising maximally within the superior medial and lateral frontal cortices, removing any doubt that these waveforms might be focally generated in deep cortical midline structures or even the thalamus, improbable historical concepts sometimes erroneously supported by modern source localization studies (Colrain, 2005). Difficulties inherent in EEG source modeling of large, distributed sources are most likely responsible for the inability of source models, especially equivalent current dipole mapping, to have accurately depicted the intracranial localization of K-complexes (Ueno and Iramina, 1990; Lu et al., 1992; Numminen et al., 1996; Colrain, 2005; Kobayashi et al., 2005; Zumsteg and Wennberg, 2005). Results of K-complex source modeling using MEG, which have found predominant sources localized to the centrotemporal or inferior parietal areas, are clearly not in keeping with the intracranial electrical field, possibly reflecting the insensitivity of MEG to a largely radial orientation of K-complex currents (Ueno and Iramina, 1990; Lu et al., 1992; Numminen et al., 1996), although this
hypothesis may not entirely explain the MEG modeling results. A detailed examination of scalp EEG and MEG K-complex source modeling will be the subject of another paper.

A recent article has provided another line of evidence that K-complexes are cortically-generated, based on microelectrode recordings obtained in lateral frontal, superior temporal and temporoparietal areas in eight patients with medically-refractory epilepsy (Cash et al., 2009). The broadband microphysiological features identified support the concept that K-complexes represent cortical “down-states”, similar to those described experimentally with slow waves of deep (stage 3 and 4) sleep (Contreras et al., 1996; Amzica and Steriade, 1998; Cash et al., 2009). This paper also presented macroelectrode data depicting the intracranial K-complex to have: (i) a surface-negative field in the occipital, parietal, inferior temporal and orbitofrontal cortices, and (ii) a simultaneous surface-positive field in the prefrontal cortex (Cash et al., 2009). However, an intracranial field with that distribution would be incompatible with the classically recognized predominance of the K-complex over the midline frontal region – a high amplitude negative field in the EEG maximal over the frontal region cannot be generated intracranially by a surface-negative field in the occipital, parietal, inferior temporal and orbitofrontal cortices and a surface-positive field in the anterior frontal cortex. Such an intracranial field would of necessity produce in the scalp EEG a posterior and inferior cranial negativity and an anterior frontal positivity.

It is difficult to ascertain how the K-complex distribution reported by Cash et al. (2009) was arrived at. Inadvertent polarity inversion of some tracings could be responsible, but no single inversion could explain all of the incorrect polarities. Reference electrode contamination is another possibility, and very little information was provided about this technical aspect of the macroelectrode recordings, only that intradural electrodes facing away from the cortex were used as references (Cash et al., 2009). No information was given as to where these electrodes were situated or to what extent they may have acted as active electrodes. One could envision intracranial reference electrode contaminations that might explain certain of the incorrect waveforms, however, no single reference electrode position could explain all of the incorrect
waveform polarities in (Cash et al., 2009). Another possibility is that the very few (one to four) scalp electrodes used may have been insufficient to accurately identify K-complexes, especially if no electrodes were placed over the frontal regions. This may have led to false identification of some non-K-complex slow waves as K-complexes. In any event, the macroelectrode findings in Cash et al. (2009) were not the primary focus of their paper, which was principally oriented toward an analysis of their cellular, microphysiological results.

It is known that both epilepsy and antiepileptic medications may affect sleep quality and structure and it is reasonable to discuss whether the K-complexes recorded in the patients in the present study are representative of K-complexes in all individuals. Various antiepileptic medications, including carbamazepine, phenytoin, valproic acid, lamotrigine, gabapentin, barbiturates and benzodiazepines, have been documented to have different effects on sleep architecture, often involving alterations in the amount of stage 2 sleep, and some of these medications have been shown to alter the abundance of K-complex and sleep spindle activity, usually in the direction of decreasing K-complex density and increasing sleep spindle density (Johnson et al., 1976; Legros and Bazil, 2003; Colrain, 2005). However, there is no evidence that the morphology (i.e., distribution, time course and amplitude) of K-complexes is altered by any of these medications. The six patients in this study were taking various combinations of nine different antiepileptic medications, and yet the scalp EEG morphology of the K-complexes was similar for all six patients – and the same as that seen in individuals without epilepsy and taking no medications. As such, it would seem most plausible that the same extended intracranial generator is responsible for the morphologically-identical K-complexes seen in all individuals on scalp EEG.

A similar line of argument can be used with respect to the related question of whether or not patients with epilepsy may have unique sites or distributions of intracranial origin for their K-complexes. The scalp EEG K-complex distributions of patients are identical to those of individuals without epilepsy, implying (notwithstanding the “inverse problem” of source
that the intracranial origins of these physiological potentials are most likely the same in persons with and without epilepsy. Many papers describing interactions between epilepsy and K-complex formation have focused on primary generalized epilepsy, which is understandable given that K-complex (and sleep spindle) generation and 3 Hz spike-and-wave generation are believed to share common neuroanatomical and neurophysiological substrates (Colrain, 2005; Maganti et al., 2005; Myatchin and Lagae, 2007). However, although alterations in sleep architecture have been noted, including decreased sleep spindle abundance, alterations in sleep complex morphology have not been described. In any event, none of the patients in this study suffered from primary generalized epilepsy, and there is as yet no recognized association between focal epileptic disorders and alterations in K-complex form. Moreover, the sites of localized seizure generation in these six patients differed so widely that it would be difficult to envision an effect of their epilepsies upon the generation of their K-complexes, especially when considering that the K-complex distribution appeared similar amongst them all, and with the same scalp distribution as seen in individuals without epilepsy. Subtle effects heretofore unrecognized may yet of course be uncovered, but these would not appear to be measurable by EEG.

Previous MEG studies have described K-complexes to be recorded with variable sites of maximal amplitude and with variable latencies in peak amplitude between different regions of involvement (Lu et al., 1992; Numminen et al., 1996). In addition, analysis of sleep slow waves using high-density scalp EEG has suggested that not only slow waves, but also K-complexes, may represent traveling waves, with a preferred direction of propagation from front to back in the brain (Massimini et al., 2004). Though not a focus of the present study, no obvious traveling propagation of K-complexes could be appreciated intracranially in either the averaged or unaveraged intracranial waveforms. Waveform amplitudes at different involved sites did show clear variations between individual K-complexes, although this may have been in part related to the superposition of K-complex waveforms and spontaneous background activity. Examination of the same waveforms after low-pass filtering at 4 Hz, done to match the filter parameters of the
high-density scalp EEG analysis (Massimini et al., 2004), likewise revealed no apparent tendency for the intracranial K-complex waveforms to propagate in a continuous fashion in any particular direction (data not shown). However, it must be acknowledged that whereas most of the averaged intracranial K-complex peaks (both negative and positive) appeared synchronously with the averaged scalp EEG maximum negative peak, at a minority of intracranial electrode sites there were evident peak latencies. This was most apparent with a small number of positive mesial waveforms, particularly the waveform recorded from the anterior cingulate gyrus in patient 1. It is not entirely clear how to best explain this peak latency. That this positive waveform could represent a secondarily generated local potential arising within the cingulate cortex, with an inverted columnar source and sink distribution, would seem highly improbable. More likely is that the positive polarity indeed represents the positive dipolar side of the extended superficial cortical dipole layer, as is seen synchronously farther away in the thalamus and inferior hemispheric cortices and subcortical white matter. However, why the peak latency around the line of polarity reversal? It is possible that a component of early negativity is present in the field recorded by the anterior cingulate electrode (FM9) and the more posterior frontal medial electrodes (FM19, FM20) and that this may shift the positive peak to the right, in which case a more inferior electrode, e.g., an electrode overlying the anterior corpus callosum, might show a positive peak with no latency. However, this is speculative. Another possible interpretation is that these mesial positive peak latencies do suggest the existence of anterior to posterior K-complex propagation: as can be seen in the potentials recorded by the inferior parietal electrodes (TP1, TP2) in patient 1 there is a corresponding surface negative peak latency over this aspect of the lateral parietal cortex. In this regard, it must be recognized that intracranial recording was not available from the superior lateral parietal cortices in the patients in this study, nor from the anterior corpus callosum, precluding further clarification with respect to either of these hypotheses. Future studies specifically looking for evidence of intracranial K-complex
propagation will hopefully provide more definitive insight into whether or not there is traveling wave propagation during sleep.

Finally, it must be recognized that from the scalp EEG topography it would have been impossible to predict that the intracranial K-complex field would reverse above the cingulate cortex, and that the cingulate gyrus would be specifically excluded from generation of the human K-complex. An early experimental study in monkeys suggested that the cingulate cortex was involved in K-complex generation, although whether the waveforms analyzed in that study were homologous to human K-complexes is unclear (Hughes and Mazurowski, 1964). From the intracranial human recordings presented here, the cingulate cortex, along with the functionally related mesial temporal structures, appear uninvolved in human K-complex generation.
Fig. 4.1. Scalp EEG recordings of K-complexes in patients 1-6, arranged in order from left (patient 1) to right (patient 6), with corresponding scalp voltage topographic maps below the averaged waveforms for each patient. Common average (12 scalp electrodes) referential montage; LFF = 0.5 Hz; HFF = 70 Hz, this and all other figures.
Fig. 4.2. Composite diagram of averaged K-complex waveforms recorded from the cortical surface and deep midline structures in six patients. (A) The K-complex field is maximal over the anterior and superior frontal region of the lateral aspect of the brain, the surface-negative field gradually diminishing posteriorly and inferiorly, ultimately reversing in polarity over the inferior temporal region. (B) On the mesial aspect of the brain, the surface-negative field is also maximal over the superior frontal region, but shows an earlier inferior polarity inversion, occurring above the cingulate gyrus. The four inferior, positive waveforms are recorded from electrodes in the thalamus, splenium of the corpus callosum, hippocampus and inferior temporal gyrus.
Fig. 4.3. Summary detail of averaged K-complexes most important for demonstrating intracranial field distribution. Magnetic resonance images show locations of patients’ recording macroelectrodes. (A) Top trace, negative waveform, superior frontal gyrus. Middle two traces, inverted, positive waveforms at depth electrode contacts in the white matter of the frontal lobe. Bottom trace, lower amplitude negative waveform, orbitofrontal cortex. (B) Top two traces, negative waveforms, mesial superior frontal gyrus. Third trace, isopotentiality overlying cingulate sulcus separating frontal gyrus from cingulate gyrus. Bottom trace, inverted, positive waveform, anterior cingulate cortex. (C) Inverted, positive waveforms at all electrode contacts within the thalamus. (D) Negative waveforms over the lateral frontal convexity. Top trace, superior frontal gyrus. Middle two traces, middle frontal gyrus. Bottom trace, inferior frontal gyrus. (E) Inverted, positive waveforms, inferior temporal gyri (top three traces) and parahippocampal gyrus (bottom trace). (F) Inverted, positive waveforms at depth electrode contacts in the white matter of the temporal lobe (top three traces) and hippocampus (bottom trace).
Fig. 4.4. Patient 1. Subdural strip electrodes implanted unilaterally overlying left frontal medial (FM), frontal lateral (FL), temporal posterior (TP), temporal anterior (TA) and temporal basal (TB) cortices. Surface-negative K-complex maximum over superior medial frontal region (FM11, FM12). Isopotentiality over anterior portion of cingulate sulcus (FM10) and reversal of field polarity to surface-positive over anterior cingulate gyrus (FM9) indicates lack of cingulate cortex involvement in K-complex generation.
Fig. 4.5. Patient 2. Subdural strip electrodes implanted unilaterally overlying left temporal posterior (TP), temporal anterior (TA) and temporal basal (TB) cortices. Depth electrode implanted in left temporal lobe (TD), deepest contact (TD1) in hippocampus. Positive K-complex waveforms in hippocampus, temporal lobe white matter and basal temporal cortex represent downward volume conduction of superior frontal, surface negative field.
Fig. 4.6. Patient 3. Subdural strip electrodes implanted bilaterally overlying frontal medial (FM), frontal lateral (FL), temporal posterior (TP), temporal anterior (TA) and temporal basal (TB) cortices. Depth electrodes implanted bilaterally in temporal lobes (TD), deepest contacts (TD1) in hippocampus. Left hemisphere recordings, left column. Right hemisphere recordings, right column. Surface-negative K-complex maximum over medial and lateral frontal cortices. Positive K-complex waveforms in hippocampus, temporal lobe white matter and basal temporal cortices represent downward volume conduction of superior, surface-negative field.
Fig. 4.7. Patient 4. Subdural strip electrodes implanted unilaterally overlying right frontal medial (FM), frontal lateral (FL), frontal anterior (FA) and frontal basal (FB) cortices. Depth electrode implanted in white matter of right frontal lobe (FD). Surface-negative K-complex maximum over superior frontal region (FL1, FL2, FL26). Positive K-complex waveforms in frontal white matter represent volume conduction from surface-negative field generated in the surrounding medial, lateral, anterior and basal frontal cortices. Waveforms over mid-posterior cingulate gyrus positive (FM15, FM16) or isopotential (FM13, FM14), indicating lack of involvement in K-complex generation.
Fig. 4.8. Patient 5. Subdural strip electrodes implanted overlying temporal posterior (TP), temporal anterior (TA) and temporal basal (TB) cortices bilaterally, and overlying right occipital temporal (OT) and left occipital posterior (OP) cortices. Depth electrodes implanted in temporal lobes (TD) bilaterally and in right occipital lobe (OD), deepest contact (OD1) in splenium of corpus callosum. Left hemisphere recordings, left column. Right hemisphere recordings, right column. Brain MRI shows right occipital encephalomalacia. Isopotentiality over occipital cortices, uninvolved in K-complex generation. Positive K-complex waveforms in temporal and occipital lobe white matter and in basal temporal cortices represent downward volume conduction of superior frontal, surface negative field.
Fig. 4.9. Patient 6. Deep brain stimulating electrode implanted in thalamus (ThD). Positive K-complex waveforms in thalamus represent downward volume conduction of superior frontal, surface-negative field.
Fig. 4.10. Eight unaveraged K-complexes in patient 1 show the intracranial variations present in individual waveforms. The cortical distribution of the K-complex field can be appreciated in the individual waveforms (maximal negativity over the superior medial frontal cortex (FM11, FM12) with reversal of field polarity over the anterior cingulate cortex (FM9)), but averaging to reduce the amplitude of the mixed frequency background activity makes the field of distribution much clearer (compare with Fig. 4.4).
Fig. 4.11. Eight unaveraged K-complexes in patient 3 show the intracranial variations present in individual waveforms. The cortical distribution of the K-complex field can be appreciated in the individual waveforms (maximal negativity over the medial (FM) and lateral (FL) frontal cortices), but averaging to reduce the amplitude of the mixed frequency background activity makes the field of distribution much clearer (compare with Fig. 4.6). L = left; R = right.
Fig. 4.12. Eight unaveraged K-complexes in patient 6 show the intrathalamic, volume conducted positive waveforms to have less variation than the cortical waveforms recorded in other patients (compare with Figs. 4.10, 4.11), possibly due to the lower amplitude of spontaneous thalamic background activity recordable with macroelectrodes.
Fig. 4.S1. Effects of different scalp reference electrode selections upon intracranial K-complex waveform morphologies, patient 1. Each column shows the averaged intracranial waveforms of the same 50 K-complexes shown in Figs. 4.1, 4.4. From left to right: first column, common average reference of 12 scalp electrodes (T3, T5, F3, C3, P3, O1, F4, C4, P4, O2, T4, T6) as described in text; second column, linked ears reference; third column, right occipital O2 electrode reference; fourth column, right surface sphenoidal Sp2 electrode reference; fifth column, midline frontocentral FCz electrode reference. Only in the last “monopolar” referential montage, where the FCz electrode is situated within the area of maximal scalp EEG K-complex negativity, does reference electrode contamination significantly affect the waveform morphologies, producing, as expected, marked changes in the scalp EEG channels (decreasing Fz negativity and inverting Cz and Pz waveforms to relative positivity), with lesser changes intracranially (decreasing the amplitude of large negative intracranial waveforms, increasing the amplitude of positive intracranial waveforms, and inverting the polarity of the low amplitude frontocentral waveforms from negative to positive).
Chapter Five

EEG and MEG in mesial temporal lobe epilepsy:

Where do the spikes really come from?

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Abstract

Objective: There is persistent debate as to whether or not EEG and MEG recordings in patients with mesial temporal lobe epilepsy (MTLE) can detect mesial temporal interictal epileptiform discharges (spikes), and this issue is particularly relevant for source localization studies. With the aim of providing direct evidence pertinent to this debate we present detailed examples of the intracranial sources of spikes recorded with EEG and MEG in MTLE.

Methods: Spikes recorded in five different patients with MTLE during intracranial EEG (n=2), intraoperative electrocorticography (ECOG; n=1), combined scalp-intracranial EEG (n=2) and combined EEG-MEG (n=1) were analyzed and the intracranial sources of the spike foci were matched with their corresponding extracranial EEG and/or MEG fields. EEG and MEG dipole source localization was performed on six independent spike foci identified in one representative patient with bilateral MTLE.

Results: Spikes with an electrical field maximal at F7/8, F9/10 ≥ T3/4 were generated in the anterolateral temporal neocortex. The absence of coincident spiking at mesial locations indicated that these were not propagated from or to the hippocampus. Spikes with an electrical field maximal at T3/4 ≥ T9/10 were generated in the lateral temporal neocortex and likewise did not involve the hippocampus. Individual spikes generated in the mesiobasal temporal neocortex, including the fusiform gyrus, were difficult to detect with EEG (low amplitude diphasic waves most apparent after spike averaging at T3/4, T9/10 ≥ T5/6, P9/10) and only slightly more identifiable with MEG. Spikes generated within and confined to the mesial temporal structures, as confirmed by intracranial recordings, could not be detected with EEG or MEG. Notably, such spikes could not be detected even at intracranial recording sites on the lateral surface of the temporal lobe.

Conclusions: We present detailed evidence in a small case series showing that typical anterior temporal spikes recorded with EEG and MEG in MTLE arose from the anterolateral temporal neocortex and were neither propagated from nor to the hippocampus. Mid temporal EEG spikes
were localized to the lateral temporal neocortex. Intracranially detected mesial temporal spikes were not detected with EEG or MEG.

Significance: The spikes recorded with EEG and MEG in MTLE are localized to neocortical foci, and not to the mesial temporal structures. Current noninvasive EEG and MEG source localization studies cannot accurately identify true mesial temporal spikes.
5.1. Introduction

There has been much debate as to whether or not interictal epileptiform activity (spikes) generated within the mesial temporal structures can be recorded extracranially with EEG and MEG, and this issue is particularly relevant for source localization studies (Ebersole and Wade, 1990; Ebersole, 1997, 2000; Boon et al., 1997; Lantz et al., 1997; Merlet et al., 1998; Shindo et al., 1998; Merlet and Gotman, 1999; Baumgartner et al., 2000; Waberski et al., 2000; Huppertz et al., 2001; Lantz et al., 2001; Shigeto et al., 2002; Gavaret et al., 2004; Michel et al., 2004a; Kobayashi et al., 2005; Stephen et al., 2005; Zumsteg et al., 2005; Plummer et al., 2007, 2008; Agirre-Arrizubieta et al., 2009). A recent paper by Kaiboriboon et al. (2010) describing spikes in mesial temporal lobe epilepsy (MTLE) provided a further addition to the debate, and the findings were interpreted as evidence that MEG can detect mesial temporal spikes. However, whereas MEG is able to detect spikes in patients with MTLE, the evidence to date has not shown conclusively that the spikes detected are actually localized to the mesial temporal structures.

For more than 50 years intracranial EEG recordings, initially using intraoperative electrocorticography (ECOG) and later supplemented with chronic intracranial EEG, have demonstrated that patients with MTLE have spikes generated independently from multiple regions of one or both temporal lobes. The intracranial spike fields have been shown to range in size from less than 1 cm² (e.g., apparent at only one contact in a row of adjacent intracranial electrodes) to more than 20 cm², with independent spikes recorded from the limbic structures of the mesial temporal region and from the anterior and/or basal and/or lateral temporal lobe neocortices (Talairach and Bancaud, 1966; Niedermeyer and Rocca, 1972; Gloor, 1975; Privitera et al., 1990; Marks et al., 1992; Quesney and Niedermeyer, 1993; Tsai et al., 1993; Wennberg et al., 1997a; Fernández Torre et al., 1999; Gavaret et al., 2004; Tao et al., 2007; Goncharova et al., 2009). It has been reported that waveforms visible with (unaveraged) scalp EEG require synchronous neuronal activity extending across at least 6 cm² of cortex (Cooper et al., 1965), and that typical temporal spikes reflect activity in large neocortical areas 10-20 cm² in size, and never
activity limited to mesial structures (Merlet and Gotman, 1999; Gavaret et al., 2004; Zumsteg et al., 2006a; Tao et al., 2007). Intraoperative ECOG and chronic intracranial EEG have demonstrated that high amplitude spikes restricted to one or more of the limbic structures in the mesial temporal region are not detected by intracranial electrode contacts situated over the lateral temporal neocortex, let alone by scalp EEG (Tsai et al., 1993; Alarcon et al., 1994; Wennberg et al., 1997a,b; Gavaret et al., 2004; Zumsteg et al., 2006a), such that one might reasonably question a priori whether noninvasive recordings could ever be expected to detect mesial temporal spikes. Nayak et al. (2004) found that only 9% of all temporal lobe spikes detected intracranially by foramen ovale electrodes were visible on scalp EEG without averaging. Similar reservations pertain to MEG, which is thought to be even less sensitive to deep sources than EEG (Mikuni et al., 1997; Baumgartner et al., 2000; Oishi et al., 2002; Rampp and Stefan, 2007). Shigeto et al. (2002) showed that mesial temporal spikes recorded by intracranial EEG were not detected by simultaneous MEG.

In the present context, it is important to recognize that most patients with MTLE will have (a) mesial temporal spikes, i.e., spikes generated within and confined to the mesial temporal structures, and (b) temporal neocortical spikes. In other words, patients with MTLE may have, and usually do have, independent spike foci involving the mesial structures and the temporal neocortices (Talairach and Bancaud, 1966; Niedermeyer and Rocca, 1972; Gloor, 1975; Privitera et al., 1990; Marks et al., 1992; Quesney and Niedermeyer, 1993; Tsai et al., 1993; Alarcon et al., 1994, 1997; Wennberg et al., 1997a; Fernández Torre et al., 1999; Gavaret et al., 2004; Tao et al., 2007; Goncharova et al., 2009). In light of the aforementioned debate, resolution of which is important for the advancement of EEG and MEG source localization in epilepsy, we aim in this paper to provide additional evidence that may serve to illuminate more clearly the true intracranial sources of the spikes recorded by EEG and MEG in patients with MTLE.
5.2. Methods

The patients presented in this study provide a representative example of the typical EEG and MEG findings in MTLE. All of the patients suffered from medically intractable MTLE and the data shown here were obtained during the course of their routine clinical investigations, as performed to determine candidacy for resective epilepsy surgery. All patients provided informed consent for all investigations. All but one of the patients had their ictal onsets entirely localized to mesial limbic structures (hippocampus or parahippocampal gyrus) of one or both temporal lobes, as documented by intracranial EEG or combined scalp-intracranial EEG (stereoelectroencephalographic) recordings. The intracranial EEG recordings were performed in these patients because noninvasive EEG and/or MEG had demonstrated bilateral anterior and/or mid temporal spikes and noninvasive ictal EEG recordings were inconclusive as to lateralization. The remaining patient had unilateral spikes and noninvasive ictal EEG onsets concordant with ipsilateral hippocampal sclerosis on brain MRI. This patient, whose intraoperative ECOG recording is presented, did not undergo intracranial EEG recording prior to surgery. All but one patient had evidence of unilateral or bilateral hippocampal sclerosis on MRI (brain MRI was normal in one patient). A summary of the patients and the recordings obtained (after initial investigations with continuous video-EEG in all patients) is shown in Table 5.1.

Intracranial EEG was recorded (XLTEK, Oakville, ON, Canada) from three bilateral 4-contact subdural strips inserted through a burrhole over the second temporal gyrus of each temporal lobe, one strip running anteriorly, one posteriorly and one inferiorly. A single 4-contact depth electrode was implanted through the same burrhole, the deepest contact aimed at the anterior hippocampus. This is a standardized implantation array at our institution used for chronic intracranial EEG monitoring in adults with bilateral temporal lobe epilepsy, the distribution of electrode contacts allowing for easy differentiation of mesial limbic versus neocortical seizure onsets. Electrode placement is guided by frameless stereotaxy and confirmed by MRI. The subdural electrodes sample anterior, basal and lateral temporal neocortices, as well as the
parahippocampal gyrus, and the depth electrode samples the anterior hippocampus, lateral temporal neocortex, and intervening white matter (Valiante, 2009).

For stereoelectroencephalographic recordings, intracranial EEG was acquired along with simultaneous scalp EEG, the latter recorded from 27 electrodes (standard 10-20 plus F9/10, T9/10, P9/10 and surface sphenoidal (zygomatic) electrodes, Sp1/2). Sampling rate was 500 Hz.

Intraoperative ECOG was performed as described previously, including chemical activation with intravenous alfentanil (Manninen et al., 1999; McGuire et al., 2003).

Simultaneous EEG/MEG was recorded using a 151-channel whole head CTF MEG system (Port Coquitlam, BC, Canada) including 19 standard 10-20 scalp EEG channels. Fifteen separate 2-minute recording segments were obtained. Sampling rate was 625 Hz.

5.2.1 Source localization

Source localization of independent temporal lobe spike foci was performed in one representative patient with bilateral MTLE who was investigated with combined scalp EEG/MEG and, one week later, with stereoelectroencephalography prior to resective surgery. A continuous 4-hour segment of combined scalp-intracranial EEG was analyzed for interictal spikes, which were manually reviewed and selected using Insight software (Persyst, Prescott, AZ, USA). Spikes with the same morphology and field of distribution were subsequently averaged and analyzed using Curry 6.0 (Abbotsford, Victoria, Australia). The discrete scalp EEG spike waveform morphologies identified in the scalp-intracranial EEG recordings provided templates to match the spikes captured during the EEG/MEG recordings, allowing for comparison of the MEG and intracranial EEG fields. MEG spikes representing the different intracranial fields were manually identified, averaged and analyzed using Curry 6.0. Realistic volume conductors (head models) were used, the Curry 6.0-inbuilt finite element interpolated model (FEMi) for scalp EEG and a high resolution boundary element model (BEM) created from the MNI averaged MRI dataset for
MEG. EEG and MEG sources were localized onto a high resolution cortex segmentation of the MNI averaged MRI dataset.

Dipole mapping using the fixed coherent dipole algorithm (surrogate for the classical equivalent current dipole model) was performed on EEG and MEG averaged spikes localized to six discrete temporal lobe areas, as identified by the intracranial recordings. Preprocessing of the averaged spike data using principal and independent component analysis (PCA, ICA) did not in general improve upon the results obtained from analysis of the unprocessed data (and was at times associated with less plausible results); these results are not shown.

5.3. Results

5.3.1. Intracranial EEG and ECOG

Intracranial EEG recordings in patients with MTLE inevitably demonstrate interictal spikes restricted to the limbic structures in the region of the uncus, hippocampus and parahippocampal gyrus. These may have different morphologies, with perhaps the two most common patterns being (a) electronegative spikes restricted to the hippocampus, and (b) electropositive spikes in the hippocampus that show simultaneous electronegativity at the mesiobasal structures around the uncus and parahippocampal gyrus (Polkey et al., 1989; Marks et al., 1992; Tsai et al., 1993). The dipolar pattern of the latter spikes is most suggestive of spike generation within the uncal or parahippocampal cortices, with the positive waveform apparent in the hippocampus likely representing the “opposite” side of the focal, volume conducted mesial temporal field. Spikes such as these, unless averaged, are not visible on scalp EEG (Merlet et al., 1998; Wennberg and Lozano, 2003; Gavaret et al., 2004; Zumsteg et al., 2006a).

Fig. 5.1 shows examples of individual and averaged spike fields in a patient (M1) with intractable MTLE and left hippocampal sclerosis. All clinical seizures were associated with left mesial temporal ictal onsets and the patient became seizure free after a left anteromesial temporal resection. Both of the common mesial temporal spike patterns are evident, and, in addition, an
independent anterolateral neocortical spike focus is apparent. This latter neocortical focus represents the type of intracranial field that is associated with anterior temporal lobe spikes recorded with scalp EEG (see below and Fig.1 in Wennberg, 2010a).

Fig. 5.2 shows examples of averaged negative and positive focal hippocampal spikes recorded in a patient (M2) with intractable MTLE and bilateral hippocampal sclerosis, investigated with stereoelectroencephalography. The only intracranial electrodes implanted in this case were orthogonal depth electrodes aimed at the anterior hippocampus. Ictal onsets associated with the patient’s usual clinical seizures were localized to the left hippocampus and the patient became seizure free after a left anteromesial temporal resection. It can be seen that averaging of multiple identical spikes can produce a volume conducted far field demonstrable with scalp EEG voltage topographic maps. However, this field is of very low amplitude (5-10 μV), even after averaging more than 30 spikes, and individual spikes of this sort could never be detected noninvasively. Indeed, it can be seen in Fig. 5.2 that the averaged electrical spike fields are not even detected by the more superficial contacts of the ipsilateral intracranial depth electrodes (TD3, TD4), which are situated in the temporal white matter and overlying lateral temporal neocortex. It is thus not surprising that the spikes are not visually apparent farther away, outside the skull, in the scalp EEG recording.

Fig. 5.3 provides another example of mesial temporal spikes that are not detected intracranially at the lateral surface of the ipsilateral temporal lobe. The figure depicts an intraoperative ECOG recording in a patient (M3) with unilateral left MTLE and left hippocampal sclerosis. The patient became seizure free after a left anteromesial temporal resection. The baseline ECOG recording shows independent anterolateral temporal neocortical spikes and mesial temporal spikes. Following chemical activation with alfentanil, the independent neocortical spikes were suppressed, as occasionally occurs (Manninen et al., 1999; McGuire et al., 2003), whereas the mesial temporal spikes were markedly, transiently increased in amplitude and abundance. It can be seen that this pronounced mesial temporal spiking remains invisible to
intracranial electrodes situated over the lateral surface of the ipsilateral temporal lobe. It would seem implausible that the electromagnetic fields associated with these classical mesial temporal spikes could be reliably detected noninvasively, using current EEG or MEG technology, when the fields cannot even be detected so near the source intracranially.

5.3.2. Propagation

Neocortical propagation of temporal lobe spikes is a phenomenon that can be identified in scalp EEG spike peak latencies (e.g., F7 to T3 or vice versa) or in travelling peak latencies evident in ECOG recordings (Alarcon et al., 1994, 1997; Baumgartner et al., 1995; Zumsteg et al., 2006b). However, direct intracranial EEG evidence of propagation between the mesial temporal structures, particularly the hippocampus, and the overlying temporal neocortex is sparse. In Fig. 5.4, we show possible evidence of mesial limbic to lateral neocortical propagation in a patient (M4) with normal brain MRI, who had clinical seizures with ictal onsets found to arise independently, with approximately equal frequency, in both mesial temporal regions, such that resective surgery was not performed. Fig. 5.4 shows the five different foci of intracranial spikes that were identified in the right temporal lobe of this patient, one of which did provide suggestive evidence of mesial limbic to lateral neocortical propagation, with positive spikes near the hippocampus and parahippocampal gyrus followed by the appearance 100-200 ms later of negative anterolateral temporal neocortical spikes. Although one cannot entirely exclude the possibility that this association was coincidental (positive limbic spikes and negative neocortical spikes were frequently recorded independently (Fig. 5.4)), their repeated occurrence with relatively constant peak latency did suggest in this case the existence of transsynaptic propagation. It must be acknowledged that in this particular spike pattern the negative side of the mesial dipolar field was not identified, presumably because the implantations of both the orthogonal depth electrode and the inferior temporal subdural strip electrode did not extend quite as far mesially as intended (Fig. 5.4).
Thus, evidence suggestive of mesial limbic to lateral neocortical propagation may on occasion be identified with intracranial EEG. However, propagation of this sort could not be identified with the three independent spike foci present in the left temporal lobe of this patient (data not shown), nor in any of the other patients in this study. Moreover, even if anterolateral temporal neocortical spikes detectable with scalp EEG were occasionally the result of spike propagation originating in the mesial temporal structures, there would be no way to confirm this without simultaneous intracranial EEG.

5.3.3. Stereoelectroencephalography, EEG/MEG and source localization

In Figs. 5.5-5.10 we present a more detailed analysis of a representative patient (M5) with intractable MTLE investigated with combined EEG/MEG and, one week later, with stereoelectroencephalography, including EEG and MEG dipole source localization of the six separate temporal neocortical foci identified during the stereoelectroencephalographic investigation. This patient had MRI evidence of right hippocampal sclerosis and clinical seizures were found to arise independently from both mesial temporal regions, but with a right-sided predominance at a ratio greater than 9:1. Right anteromesial temporal lobe resection has resulted in an Engel Class IC outcome (two disabling seizures during first post-operative year, then seizure free for more than two years).

The stereoelectroencephalographic recordings allowed us to identify six distinct, independent neocortical temporal lobe spike foci along with their corresponding extracranial EEG and MEG fields: right anterolateral (Fig. 5.5), right mesiobasal (Fig. 5.6), left anterolateral (Fig.5.7), left anterobasolateral, with evidence of fast anterior to posterior neocortical propagation (Fig. 5.8), left lateral (Fig. 5.9), and left mesiobasal (Fig. 5.10).

As with other patients investigated with stereoelectroencephalography (e.g., patient M2, this study; Merlet and Gotman, 1999; Wennberg, 2010a), focal negative intracranial spikes with an electrical field essentially restricted to the depth electrode contact nearest the hippocampal
formation could not be identified on the scalp EEG without averaging of multiple spikes. These mesial spikes were thus not used for EEG or MEG source localization as their fields were both too small and too deep to be detected by the noninvasive recordings. All MEG spike fields could be attributed to one of the six neocortical areas identified by intracranial EEG, and thus there did not appear to be any MEG representation of deep focal spikes generated within the limbic structures of the hippocampus, consistent with the previously described findings of Shigeto et al. (2002).

Spikes with an electrical field maximal at F7/8, F9/10, Sp1/2 ≥ T3/4 were generated in the anterolateral temporal neocortex (Figs. 5.5, 5.7). They were not propagated from or to the hippocampus. The larger anterobasolateral intracranial spike field was associated with a correspondingly larger scalp EEG distribution that extended to also involve T9, P9 > T5, and the fast intracranial anterior to posterior spike propagation just visible from TA1 to TA2 and TA2 to TA3, TA4 is evident extracranially from F7, F9 to T3, T9 to T5, P9 (Fig. 4.8). Spikes with an electrical field maximal at T3, T9 > T5, P9 > F7, F9, Sp1 were generated in the lateral temporal neocortex, with the negative generator side of the dipolar field detected with scalp EEG presumably situated just lateral to the most superficial contact of the orthogonal intracranial depth electrode (TD4), on the surface of the lateral temporal neocortex (Fig. 5.9). Spikes generated in the mesiobasal temporal neocortex, including the fusiform gyrus, were barely visible with EEG, even after averaging, and appeared as low amplitude diphasic waves best seen at T3/4, T9/10 ≥ T5/6, P9/10; the corresponding MEG waveforms appeared slightly more identifiable, especially after averaging (Figs. 5.6, 5.10).

The EEG dipole source localization results provided reasonable solutions for the different foci, with horizontal temporal tip localizations for the anterolateral spike foci (Figs. 5.5, 5.7), horizontal anterior temporal solutions for the anterobasolateral and lateral spike foci (Fig. 5.8, 5.9) and vertical anterior temporal localizations for the mesiobasal spike foci (Figs. 5.6, 5.10). The propensity for anterior temporal tip localizations and the usefulness of horizontal versus
vertical dipole orientation in differentiating lateral from mesiobasal intralobar sources has been repeatedly discussed (Baumgartner et al., 2000; Pataara et al., 2005; Ebersole and Hawes-Ebersole, 2007; Kaiboriboon et al., 2010).

The MEG dipole source localization results were often comparable to the EEG solutions, despite the lower number of spikes available for averaging, although dipole orientations were not always identical and the left anterolateral temporal spike focus was falsely localized anteriorly and medially to the ipsilateral frontal lobe (Fig. 5.7).

5.4. Discussion

The detection of temporal lobe spikes with EEG (or MEG) in a patient with complex partial seizures, especially if combined with MRI evidence of hippocampal sclerosis and/or a history of febrile convulsions, is usually enough to secure the correct clinical diagnosis of MTLE. It is easy to forget that the spikes recorded with EEG and MEG likely do not arise in the mesial temporal structures, but are instead generated centimeters away in the overlying temporal neocortex. This represents an unexplained paradox in the clinical neurophysiology of MTLE, presumably indicative of the involvement of a complex electrophysiological network comprising multiple temporal lobe structures, the specifics of which remain unknown. For clinical purposes, this paradoxical situation can be safely ignored. However, for source localization studies, a clinical diagnosis of MTLE cannot be used to infer that temporal lobe spikes recorded with EEG and MEG arise from the mesial temporal region.

In this paper, we have expressly chosen to present detailed images of the spikes recorded in a small series of patients with MTLE (rather than, for example, tabulated summaries of a larger series of patients) in the hope that this sort of direct visual evidence may help to erase persistent misconceptions as to where the spikes detected with EEG and MEG in MTLE really come from. We believe these patients provide typical examples of MTLE, and we have consistently found the same spectrum of independent mesial limbic and neocortical spike foci in other patients with
MTLE that have undergone similar intracranial EEG investigations at our institution. The issues and questions for which we have presented illustrative data are discussed below.

5.4.1. Can focal mesial temporal (limbic) spikes be detected with noninvasive EEG or MEG?

Many previous reports have provided empirical or theoretical evidence that spikes restricted to the mesial temporal structures are not detected with EEG or MEG (Alarcon et al., 1994; Mikuni et al., 1997; Merlet and Gotman, 1999; Baumgartner et al., 2000; Oishi et al., 2002; Shigeto et al., 2002; Gavaret et al., 2004; Nayak et al., 2004; Zumsteg et al., 2006a; Tao et al., 2007). Alarcon et al. (1994), based on empirical data, calculated a current dipole strength on the order of 2 nA·m for a typical intracranially recorded hippocampal spike, which would produce a volume conducted scalp peak voltage of 0.45 µV (and an 88 fT peak MEG field), far too small to be detected above the baseline background activity. Assuming the same estimate of current density, a 100µV temporal lobe scalp EEG spike would require a mesial temporal focal dipole strength of approximately 100-600 nA·m – equivalent to an 80 mV hippocampal spike, approximately two orders of magnitude greater in amplitude than any spike recorded in the human brain (Alarcon et al., 1994). With respect to source localization, dipole modeling results localizing EEG or MEG spikes to the mesial temporal region have calculated hypothetical hippocampal dipole strengths of 300-600 nA·m, which are not compatible with a highly focal source in the hippocampus, and do not correspond to the empirical data derived from intracranial EEG (Alarcon et al., 1994). Similarly, simulation studies have estimated that current densities must be on the order of 10-100 nA·m/mm² to create a measurable extracranial EEG or MEG field, which are up to two orders of magnitude higher than typical values cited in the literature (Alarcon et al., 1994; Stephen et al., 2005).

Nevertheless, source localization algorithms applied to visible EEG or MEG spikes showing mesial temporal solutions have been interpreted to indicate that the extracranially visible spikes may be generated within the deep mesial temporal structures (Boon et al., 1997; Lantz et
al., 1997; Merlet et al., 1998; Plummer et al., 2007, 2008; Kaiboriboon et al., 2010), something that appears at odds with simple visual analysis of the intracranial fields associated with extracranial EEG and MEG spike fields in MTLE.

In keeping with the previously cited reports showing mesial temporal spikes to be undetectable with noninvasive EEG and MEG, we have provided a number of additional examples that show this to be true, and which highlight the fact that these spikes are not even detectable by intracranial electrodes situated within the skull on the lateral surface of the temporal lobe (Figs. 5.1-5.4). Based on the empirical evidence, it appears that true mesial temporal spikes, generated within and confined to the mesial temporal structures, cannot be detected extracranially using current EEG or MEG technology.

Mesial temporal spikes detected with intracranial EEG can be averaged (on the intracranial potential) to produce volume conducted low amplitude far fields measurable in simultaneously acquired scalp EEG recordings, and the sources of these averaged far field potentials can be accurately modeled to the mesial temporal regions (Nayak et al., 2004; Zumsteg et al., 2005). However, individual mesial temporal spikes seem undetectable with EEG or MEG in the absence of simultaneous intracranial EEG. Therefore, it follows that mesial temporal dipole solutions presented in source localization studies based entirely on noninvasive EEG or MEG cannot be taken as evidence of spike localization to the mesial temporal structures – the mesial solutions may be spurious.

5.4.2. Where do the typical anterior-mid temporal spikes come from?

We have provided clear evidence that the typical anterior temporal lobe spikes recorded with EEG and MEG, which show a scalp EEG maximum at F7/F8 or equipotentiality between F7-T3/F8-T4, are generated by a widespread synchronous source involving the anterolateral temporal neocortex, with no involvement of the ipsilateral limbic structures. In other words, the spikes are not only not localized to the mesial temporal structures, they may be independent of
any involvement at all of the same mesial temporal structures. The spikes are therefore not necessarily propagated to or from the hippocampus, as is often stated or presumed. This can be appreciated in Fig. 5.5, Fig. 5.7 and Fig. 5.8 (and in Fig. 1 of Wennberg, 2010a), where there is seen to be no involvement of the hippocampus (apart from the volume conducted field representing the positive end of the anterior temporal neocortical dipole layer). We furthermore show that mid temporal EEG spikes maximal at T3/4 ≥ T9/10 are generated in the lateral temporal neocortex, and likewise do not involve the mesial temporal structures (Fig. 5.9).

We have also shown that spikes generated in the mesiobasal temporal neocortex are difficult to detect with EEG (appearing as low amplitude diphasic waves best seen with spike averaging at T3/4, T9/10 ≥ T5/6, P9/10) and only slightly more identifiable with MEG (Figs. 5.6, 5.10). Detection of individual spikes with this topographic field is difficult in the absence of simultaneous intracranial EEG, as has been previously reported by Nayak et al. (2004), who also described low amplitude EEG spikes over the lateral subtemporal surface as the extracranial manifestation of mesiobasal temporal spikes. It should be noted that even though the low amplitude spikes with this field arise from a source that is mesially situated in comparison to the neocortical source of classical anterior temporal spikes, these spikes do not represent true mesial temporal (limbic) spikes in that they are distributed laterally over the basal temporal neocortex, typically including the fusiform gyrus.

5.4.3. Can dipole modeling provide reasonable source solutions for temporal lobe spikes?

The EEG and MEG dipole source localization results in this paper are shown for illustrative purposes, with the solutions for the averaged spike fields for the most part in keeping with accepted anterior temporal horizontal orientations for anterolateral and lateral neocortical sources and vertical orientations for mesiobasal sources (Baumgartner et al., 2000; Pataaraia et al., 2005; Ebersole and Hawes-Ebersole, 2007; Kaiboriboon et al., 2010). It must be emphasized that Figs. 5.5-5.10 depict the results of source localization performed on averaged neocortical spikes.
that were grouped only after detailed analyses of their intracranial and corresponding extracranial
topographic fields, producing a significant benefit in signal-to-noise ratio. However, in clinical
recordings, it is not usually possible to average as many spikes as were available in this patient. In
a separate analysis of the same MEG data, dipole mapping of unaveraged spikes produced
reasonably good lobar localizations (<10% of spikes falsely localized to frontal or insular
structures) and scattered intralobar solutions, including some dipoles localized to the mesial
temporal regions bilaterally (Supplementary Fig. 5.S1). Dipole source localization of individual
spikes is dependent on many factors including signal-to-noise ratio, background frequency,
applied filters, selected forward and inverse models, all in addition to the distribution of the true
intracranial sources. A particularly relevant problem is the propensity toward inappropriately
deep subcortical dipole solutions for large superficial cortical sources (Alarcon et al., 1994;
Gavaret et al., 2004; Plummer et al., 2008), which likely explains the deep mesial solutions
occasionally provided for high amplitude anterior temporal spikes.

5.4.4. Are typical anterior-mid temporal spikes propagated from the mesial temporal region?

Propagation of temporal lobe spikes has been frequently described and mesial limbic to
lateral neocortical propagation is often inferred to underlie the generation of spikes recorded with
EEG and MEG in MTLE (Baumgartner et al., 1995; Ebersole et al., 1995; Ebner and Hoppe,
1995; Fuchs et al., 1999; Merlet and Gotman, 1999; Scherg et al., 1999; Lantz et al., 2003;
Pataraja et al., 2005; Zumsteg et al., 2006b; Ebersole and Hawes-Ebersole, 2007; Kobayashi et
al., 2009; Kaiboriboon et al., 2010). That temporal lobe spike propagation occurs is undeniable
and we have provided images of both fast neocortical propagation, which is relatively common
(Fig. 5.8), and (possibly) slow mesial limbic to lateral neocortical propagation (Fig. 5.4). Among
the five patients in this study, anterior and lateral temporal neocortical spikes large enough in
amplitude and extent to be detected by (unaveraged) scalp EEG were preceded by mesial limbic
spikes in only one patient, and even then infrequently. It must be acknowledged that, as with all
intracranial EEG recordings, incomplete spatial sampling, especially in the region of the amygdala, may have caused us to under-identify examples of mesial to lateral spike propagation. However, our findings are in keeping with previous studies using different intracranial EEG recording arrays, which have also demonstrated independence of mesial and lateral neocortical temporal lobe spikes (Alarcon et al., 1994, 1997; Wennberg et al., 1997a,b; Merlet and Gotman, 1999; Gavaret et al., 2004). Thus, whereas fast propagation along adjacent neocortical surfaces may be quite common, in our experience with these and other patients, evidence of mesial limbic to neocortical propagation is an exception to the general rule that neocortical spikes recorded in patients with MTLE appear, at the level accessible to detection by intracranial EEG electrodes, independent of any requirement for hippocampal input.

It may be mentioned at this point, with respect to the pathophysiology and neurophysiology of MTLE, that a speculative interpretation linking mesial and lateral neocortical spikes conceptualizes mesial limbic spikes to “activate” a temporal lobe network that includes lateral temporal neocortical structures, and that the latter may become sites of independent spiking through a process that might best be described as intralobar secondary epileptogenesis (Morrell, 1985, 1989; Wennberg et al., 1997a). However, even if the development of neocortical spike foci in MTLE is, at root and over time, related to neurophysiologic abnormalities first limited to mesial temporal structures (an unproven hypothesis), this does not impact upon the main focus of this paper, which aims to delineate the intracranial sources of temporal lobe spikes and their associated EEG and MEG fields, as recorded in patients with chronic, medically intractable MTLE.

The lack of dependency on hippocampal drive for the generation of neocortical spikes in MTLE is not surprising if one considers the longstanding observation that a patient’s typical temporal neocortical spikes are not only not abolished but indeed can become more abundant after selective surgical resection of the ipsilateral mesial temporal structures (Niemeyer, 1958; Cendes et al., 1993; Wennberg et al., 1997b). In any event, with respect to noninvasive EEG and
MEG, even if in some patients anterolateral temporal neocortical spikes might be the result of spike propagation (or “activation”) originating in the mesial temporal structures, there would be no way to know that this had occurred without simultaneous intracranial EEG. Thus, classical high amplitude anterior temporal (F7/8 > T3/4) EEG spikes, such as shown in Fig. 1 and Fig. 2 (top panel) of (Kaiboriboon et al., 2010), cannot be used to infer localization to the mesial temporal structures, no matter what solutions are provided by EEG or MEG source localization. The empirical evidence suggests that these high amplitude spikes do not have an intracranial source confined to the mesial temporal structures, nor are they necessarily the result of propagation from the mesial temporal region.

As a final comment on the conflation of MTLE with mesial temporal spikes, it must be remembered that the existence and persistence of temporal lobe neocortical spikes is not related to the likelihood of seizure freedom after surgical resection of the mesial temporal lobe structures in patients with ictal onsets confined to those mesial temporal regions (i.e., patients with MTLE) (Wennberg et al., 1997a,b). This implies that using seizure freedom after a temporal lobe resection as a standard by which to presume a mesial temporal localization of noninvasively recorded, preresection temporal lobe spikes, as has often been done in source localization studies (Waberski et al., 2000; Huppertz et al., 2001; Michel et al., 2004b), is not a particularly reasonable method (Zumsteg et al., 2005; Plummer et al., 2008). There is only one standard available to accurately delineate a mesial temporal spike localization, and that is invasive intracranial EEG (Gavaret et al., 2004; Plummer et al., 2007, 2008).

In conclusion, we hope that the evidence and arguments presented in this paper may serve to better illuminate the intracranial sources of the temporal lobe spikes recorded with EEG and MEG in MTLE. We encourage replication of these observations and reflection on this paradox concerning the clinical neurophysiology of MTLE: that the EEG and MEG spikes we routinely record are localized not to the mesial temporal lobe but rather to the temporal neocortex situated many centimeters away.
Table 5.1. Summary of patients and recordings.

<table>
<thead>
<tr>
<th>Patient</th>
<th>MRI</th>
<th>ICEEG</th>
<th>ECOG</th>
<th>SEEG</th>
<th>EEG/MEG, source modeling</th>
<th>Surgery</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>M1</td>
<td>L MTS</td>
<td>Yes</td>
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<td>-</td>
<td>-</td>
<td>L AmTR</td>
<td>IA</td>
</tr>
<tr>
<td>M2</td>
<td>B MTS</td>
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<td>-</td>
<td>Yes</td>
<td>-</td>
<td>L AmTR</td>
<td>IA</td>
</tr>
<tr>
<td>M3</td>
<td>L MTS</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>L AmTR</td>
<td>IA</td>
</tr>
<tr>
<td>M4</td>
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<td>-</td>
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<td>M5</td>
<td>R MTS</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
<td>Yes</td>
<td>R AmTR</td>
<td>IC</td>
</tr>
</tbody>
</table>

AmTR=anteromesial temporal resection, B=bilateral, ECOG=acute intraoperative electrocorticography, ICEEG=chronic depth/subdural electrode intracranial electroencephalography, L=left, MTS=mesial temporal sclerosis, R=right, SEEG=stereoelectroencephalography
Figure 5.1
Fig. 5.1. Intracranial EEG recordings obtained during presurgical clinical investigations in a patient with MTLE and left hippocampal sclerosis. Top. Shown from left to right are 5 individual electronegative mesial temporal spikes restricted to the hippocampus (depth electrode contact TD1) followed by an average of the 5 spikes. Middle. Shown from left to right are 5 individual mesial temporal spikes with a dipolar field electronegative at the uncus (subdural electrode contact TB1) and electropositive at the hippocampus (TD1). Bottom. Shown from left to right are 5 individual temporal neocortical spikes followed by an average of the 5 spikes. The spikes appear maximal over the anterolateral temporal neocortex (subdural electrode contacts TA4>3>2 and lateral depth electrode contact TD4), the negative field extending to involve the basolateral aspect of the temporal lobe (TB4). Positive waveforms appear synchronously at the electrode contacts in the white matter and mesial temporal region (TD3>2>1, TB1,2), the inverted polarity indicating that depth contacts TD1-3 and subdural contacts TB1,2 are “seeing” the opposite, positive dipole side of the spikes generated within the anterolateralobasal temporal neocortex. This is the type of intracranial spike field associated with anterior temporal spikes on scalp EEG (see Fig. 1 in Wennberg, 2010a). MR images of the left temporal lobe show the positions of intracranial 4-contact subdural electrodes overlying the anterolateral (TA1-4, contact 1 most mesial), basal (TB1-4, contact 1 most mesial) and posterior (TP1-4, contact 1 most posterior) temporal neocortices, as well as an orthogonally implanted 4-contact depth electrode aimed at the anterior hippocampus (TD1-4, contact 1 most mesial). Referential montage, scalp vertex reference electrode. LFF 0.5 Hz, HFF 70 Hz.
Stereoelectroencephalographic recordings obtained during presurgical clinical investigations in a patient with MTLE and bilateral hippocampal sclerosis, left greater than right. Shown are averaged mesial temporal spikes detected at the deepest contact (TD1) of orthogonally implanted depth electrodes aimed at the anterior hippocampi, along with their corresponding scalp EEG fields. *Left.* Electronegative left hippocampal spikes (n=43). *Middle.* Electronegative right hippocampal spikes (n=32). *Right.* Electropositive right hippocampal spikes (n=30). Shown beneath each column is the corresponding scalp voltage topographic map. Although the averaged spikes are not visible in the scalp EEG at the typical sensitivity setting shown (10 μV/mm), voltage topographic mapping does reveal a very low amplitude, volume conducted far field at the scalp for each of the 3 spike patterns, with maximal peak amplitudes between 8.0-9.5 μV.

Common average reference montage for both scalp and intracranial EEG, the average reference comprising 12 scalp electrodes (F3, F4, C3, C4, P3, P4, O1, O2, T3, T4, T5, T6); LFF 0.5 Hz, HFF 70 Hz.
**Fig. 5.3.** Intraoperative ECOG recording prior to left anteromesial temporal resection in a patient with MTLE and left hippocampal sclerosis. This patient was not investigated with intracranial EEG prior to surgery. ECOG recorded from a 6-contact subdural strip electrode situated above the Sylvian fissure (1-6, contact 1 most anterior), two 8-contact subdural strip electrodes on the superior (7-14, contact 7 most anterior) and inferior (15-22, contact 15 most anterior) lateral temporal neocortices, and two 4-contact depth electrodes inserted orthogonally through the middle temporal gyrus aimed at the amygdala (A1-4, contact A1 most mesial) and anterior hippocampus (H1-4, contact H1 most mesial). *Top.* Baseline ECOG shows negative and positive mesial temporal spikes (A1>2, H1>2) and independent anterolateral neocortical spikes (8,16>7,9,15,17; examples marked at vertical lines). *Bottom.* ECOG two minutes after intravenous bolus of alfentanil shows activation of mesial temporal spikes and suppression of independent temporal neocortical spikes. Despite their high amplitude the mesial temporal spikes are not visible at the subdural electrode contacts on the lateral temporal neocortex. Referential montage, scalp muscle reference electrode. LFF 0.5 Hz, HFF 70 Hz.
**Fig. 5.4.** Intracranial EEG recordings obtained during presurgical clinical investigations in a patient with MTLE and normal brain MRI. *Top.* Shown from left to right are averaged spikes with 5 different intracranial patterns identified in the patient’s right temporal lobe: negative mesial (TD1>TB1; n=29); positive mesial (TD1>TB1; n=24); positive mesial propagated to anterolateral neocortical (TA1-4; n=39); non-propagated negative anterolateral neocortical (TA1-4) with an inverted positive field situated posteriorly and inferiorly (TD4>3>2>1, TB3-4; n=34); positive (TD3>4) and negative (TP4) lateral neocortical (n=24). *Middle.* Shown from left to right are 5 individual spikes from the mesial to anterolateral propagated pattern (third from left in top row) followed by an average of the 5 spikes. *Bottom.* Shown from left to right are 5 individual spikes from the non-propagated anterolateral neocortical pattern (second from right in top row) followed by an average of the 5 spikes. MR images of the right temporal lobe show the positions of intracranial 4-contact subdural electrodes overlying the anterolateral (TA1-4, contact 1 most mesial), basal (TB1-4, contact 1 most mesial) and posterior (TP1-4, contact 1 most posterior) temporal neocortices, as well as an orthogonally implanted 4-contact depth electrode aimed at the anterior hippocampus (TD1-4, contact 1 most mesial). Referential montage, scalp vertex reference electrode. LFF 0.5 Hz, HFF 70 Hz.
Figure 5.5A
Fig. 5.5. (A) Stereoelectroencephalographic recordings obtained during presurgical clinical investigations in a patient with MTLE and right hippocampal sclerosis. Right anterolateral temporal spike focus. Spikes averaged on intracranial contact with maximal peak amplitude (RTA2; n=142). This entirely neocortical spike localization is associated with a classical anterior temporal scalp EEG spike field at F8, F10, Sp2. EEG source localization of the averaged spikes provides a temporal tip horizontal dipole solution (surrounded by its confidence ellipsoid volume). Sensitivity 70 $\mu$V/mm for intracranial EEG, 10 $\mu$V/mm for scalp EEG; bandpass filter 0.5-70 Hz; common average reference (as described in Fig. 5.2) for both scalp and intracranial EEG (this and all subsequent figures). (B) EEG/MEG topographic maps for averaged spike fields of the same right anterolateral temporal focus (n=108) and corresponding MEG dipole source localization of the averaged spike field.
Figure 5.6A
Fig. 5.6B. (A) Right mesiobasal temporal spike focus (same patient as Fig. 5.5). These spikes produce a very low amplitude lateral temporal scalp EEG spike field maximal at T10, P10, T4, T6, which is difficult to detect even after spike averaging (n=203). EEG source localization of the averaged spikes provides an anterior temporal vertical dipole solution. (B) EEG/MEG topographic maps for averaged spike fields of the same right mesiobasal temporal focus (n=32) and corresponding MEG dipole source localization of the averaged spike field.
Figure 5.7A
Fig. 5.7. (A) Left anterolateral temporal spike focus (same patient as Fig. 5.5). This entirely neocortical spike localization is associated with a classical anterior temporal scalp EEG spike field at F7, F9, Sp1 > T3. EEG source localization of the averaged spikes (n=48) provides a temporal tip horizontal dipole solution. (B) EEG/MEG topographic maps for averaged spike fields of the same left anterolateral temporal focus (n=4) and corresponding MEG dipole source localization of the averaged spike field, which in this case is mislocalized to the frontal lobe.
Figure 5.8A
Fig. 5.8. (A) Left anterobasolateral temporal spike focus (same patient as Fig. 5.5). This entirely neocortical spike localization is associated with a larger, anterior-mid temporal scalp EEG spike field at F7, F9, T3, T9, Sp1 > T5, P9, that is seen to propagate rapidly over the lateral neocortex in an anterior to posterior direction (LTA1 leading LTA2, F7 leading T3). EEG source localization of the averaged spikes (n=29) provides an anterior temporal horizontal dipole solution. (B) EEG/MEG topographic maps for averaged spike fields of the same left anterobasolateral temporal focus (n=5) and corresponding MEG dipole source localization of the averaged spike field.
Figure 5.9B

(A) Left lateral temporal spike focus (same patient as Fig. 5.5). This entirely neocortical spike localization is associated with a mid temporal scalp EEG spike field at T3, T9 > T5, P9 > F7, F9, Sp1. EEG source localization of the averaged spikes (n=18) provides an anterior temporal horizontal dipole solution similar to that provided for the anterobasolateral focus in Fig. 5.8. (B) EEG/MEG topographic maps for averaged spike fields of the same left lateral temporal focus (n=9) and corresponding MEG dipole source localization of the averaged spike field.
Figure 5.10A
Fig. 5.10. (A) Left mesiobasal temporal spike focus (same patient as Fig. 5.5). These spikes produce a very low amplitude lateral temporal scalp EEG spike field maximal at T9, P9, T3, T5, which is difficult to detect even after spike averaging (n=216). EEG source localization of the averaged spikes provides an anterior temporal vertical dipole solution. (B) EEG/MEG topographic maps for averaged spike fields of the same right mesiobasal temporal focus (n=4) and corresponding MEG dipole source localization of the averaged spike field.
Supplementary data to: EEG and MEG in mesial temporal lobe epilepsy: where do the spikes really come from?

Fig. 5.S1. MEG equivalent current dipole source localization results obtained using CTF software algorithm (Port Coquitlam, BC, Canada) applied to individual, unaveraged spikes (same patient, same MEG recording as Figs. 5.5-5.10). Dipole solutions scattered in both anterior temporal lobes, medially and laterally, with a large cluster of right anterior temporal dipoles. A small number of dipoles mislocalized to the frontal lobe or insula. In this figure axial MRI images show right side of brain on left side of figure.
Chapter Six

On noninvasive source imaging of the human K-complex

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Abstract

Objective: To assess whether existing noninvasive source localization techniques can provide valid solutions for large extended cortical sources we tested the capability of various methods of EEG source imaging (ESI) and magnetic source imaging (MSI) to localize the large superficial cortical generator of the human K-complex.

Methods: We recently determined the intracranial distribution of the K-complex in a study of 6 patients with epilepsy (Clin. Neurophysiol. 121 (2010) 1176). Here we use the simultaneously acquired scalp EEG data to evaluate the validity and reliability of different ESI techniques. MEG recordings were acquired in 3 of the 6 patients, and K-complexes were recorded with high density EEG and MEG in an additional subject without epilepsy. ESI forward models included finite element method and boundary element method (BEM) volume conductors; for MSI, single sphere and BEM models were assessed. Inverse models included equivalent current dipole mapping and distributed current source modeling algorithms.

Results: ESI and MSI provided physiologically invalid source solutions in all subjects, incorrectly localizing K-complex generators to deep midline structures. ESI provided consistent localization results across subjects for individual and averaged K-complexes, indicating solutions were not influenced by random noise or choice of model parameters. MEG K-complexes were lower in amplitude relative to baseline than EEG K-complexes, with less consistent localization results even after signal averaging, likely due to MEG-specific signal cancellation and sensitivity to source orientation. Distributed source modeling did not resolve the known problem of excessively deep fitting of single dipole locations for extended cortical sources.

Conclusions: Various noninvasive ESI and MSI techniques tested did not provide localization results for individual or averaged K-complexes that were physiologically meaningful or concordant with source locations indicated by intracranial recordings. Distributed source algorithms, though theoretically more appropriate for localizing extended cortical sources, showed the same propensity as dipole mapping to provide deep midline solutions for an extended
superficial cortical source. Further studies are needed to determine appropriate modeling approaches for these large electrographic events.

_Significance:_ Existing noninvasive source localization techniques may not provide valid solutions for large extended cortical sources such as the human K-complex.
6.1. Introduction

The application of EEG and MEG source imaging to the human K-complex has produced conflicting and occasionally implausible results (Ueno and Iramina, 1990; Lu et al., 1992; Iramina and Ueno, 1996; Numminen et al., 1996; Colrain, 2005).

We have recently described the cortical distribution of the main surface negative peak of the K-complex based on intracranial EEG recording in patients with intractable epilepsy (Wennberg, 2010b). In short, compatible with the classic known frontal midline maximum of the scalp EEG K-complex (Davis et al., 1939; Brazier, 1949; Roth et al., 1956), the maximal intracranial field is found over the midline frontal regions, the field reversing medially above the cingulate gyrus and laterally above the inferior temporal gyrus (Wennberg, 2010b). Polarity is reversed within the white matter of the frontal lobes, as well as in more distant subcortical structures, confirming cortical generation within the anterior and superior frontal lobe cortices (Fig. 6.1).

The surface negative peak of the K-complex (sometimes referred to as the N550) is the highest amplitude potential in the normal human EEG (Loomis et al., 1938; Roth et al., 1956; Colrain, 2005). Paradoxically, at the cellular level, it is associated with a widespread cortical down-state characterized by suppression of neuronal activity (Amzica and Steriade, 2002; Cash et al., 2009; Cserca et al., 2010; Dalal et al., 2010; Le Van Quyen et al., 2010). The polarity distribution of the intracranial K-complex electric field is consistent with the classical dipole layer model presumed to underlie generation of most (and certainly all large amplitude) potentials in the EEG (Gloor, 1985; Amzica and Steriade, 1998; Wennberg, 2010b). In line with the dipole layer model, the surface negative peak of the K-complex must represent the effects of either: (a) summated excitatory post-synaptic potential (EPSP) inputs to the superficial apical dendrites of frontal lobe cortical pyramidal cells, or (b) summated inhibitory post-synaptic potential (IPSP) inputs at the deeper cell soma level of these same pyramidal cells. The bulk of the available evidence obtained from animal and human microelectrode recordings supports the second option:
i.e., that synchronized hyperpolarizing IPSPs synapsing on pyramidal cell bodies in deeper layers of the cortical mantle are primarily responsible for initiation of the principal negative wave of the K-complex (Cash et al., 2009; Cserca et al., 2010; Dalal et al., 2010; Le Van Quyen et al., 2010).

The localization of the presumptive inhibitory inputs is unknown; however, it is reasonable to implicate the thalamus (and possibly other subcortical structures) given the known involvement of reciprocal thalamocortical circuits in slow oscillatory sleep patterns (Amzica and Steriade, 1998, 2002; Steriade and Amzica, 1998). The paucity of cortical neuronal activity during the K-complex down-state suggests that cortical contributions to the inhibitory inputs may be less likely.

The extent and timing of synchronization during the negative K-complex peak is also incompletely understood. Does cortical synchronization arise from synchrony of the subcortical hyperpolarizing IPSPs synapsing simultaneously on the soma of the relevant frontal lobe cortical pyramidal cells? Or, once initiated in one cortical region, does the K-complex propagate across the cortex, either through synaptic transmission similar to sleep slow wave propagation (Amzica and Steriade, 1995) or perhaps even as a result of endogenous electric field activity (Fröhlich and McCormick, 2010)? If synaptic propagation occurs, would it originate at the inhibitory input neurons (e.g., within the thalamus) or would it arise from corticocortical connectivity? It has been hypothesized, based on high density scalp EEG recordings and noninvasive source localization, that sleep slow waves and K-complexes may represent traveling waves propagating across the cortical surface, usually from front to back, guided along a deep interhemispheric “cingulate highway” (Massimini et al., 2004; Murphy et al., 2009). However, in intracranial EEG recordings, we could find no definite evidence to support the hypothesis of K-complexes as traveling waves, and indeed the cingulate gyrus appeared uninvolved in K-complex generation (Wennberg, 2010b). Nevertheless, in some individuals, K-complexes do at times show anterior-posterior time lags of wave onsets or peak maxima in scalp EEG recordings, and this is an unexplained phenomenon.
Recent fMRI studies have correlated K-complexes with positive blood oxygen level-dependent (BOLD) signal changes in subcortical (brainstem and thalamus) and cortical regions, the latter involving mainly paracentral, posterior and inferior parieto-occipital, superior temporal, and midline cingulate and paracingulate structures (Caporro et al., 2012; Jahnke et al., 2012). It is of interest to note that the areas of BOLD changes fairly accurately demarcate the areas of cortex not involved in generation of the negative wave of the EEG K-complex. It is conceivable that the subcortical (and perhaps even the cingulate) BOLD changes might reflect the source(s) of the inhibitory neuronal activity acting upon frontal pyramidal cell bodies to produce the negative wave of the K-complex. However, the other (predominantly posterior and inferior) cortical areas of BOLD changes, situated as they are outside the (anterior and superior) cortical areas of K-complex generation, are most likely representative of increased neuronal activity during the subsequent up-state associated with the later, lower amplitude, positive wave of the K-complex (the temporal resolution of fMRI being insufficient to identify neuronal activity confined to any single wave component of the K-complex; Jahnke et al., 2012). Thus, perhaps unexpectedly, fMRI studies have revealed no K-complex associated BOLD changes in the large frontal cortical areas responsible for generation of the highest amplitude potential in the human EEG.

The burgeoning research interest in sleep neurophysiology is certain to be accompanied by increasing attempts to incorporate noninvasive EEG and MEG source localization techniques to study various aspects of the K-complex, and it will be important to resolve whether or not these techniques are able to accurately depict the brain areas involved in K-complex generation. Previous reports describing EEG or MEG source localization of the K-complex using dipole mapping or, in one case, distributed source modeling, presented various source solutions in deep centrotemporal (Ueno and Iramina, 1990; Iramina and Ueno, 1996), inferior parietal (Lu et al., 1992) or frontal and parietal areas (Numminen et al., 1996), all of which are at odds with the true cortical localization of the intracranially recorded K-complex electric field (Wennberg, 2010b).
One particular problem for noninvasive source localization of the K-complex is the inherent tendency of inverse models to provide deep interhemispheric solutions for large, bilaterally synchronous cortical sources (Nunez, 1990; Romani and Pizzella, 1990; Hämäläinen et al., 1993; Numminen et al., 1996; Colrain, 2005; Kobayashi et al., 2005; Zumsteg and Wennberg, 2005). This may be especially relevant to source localization using single equivalent current dipole models, although it is unclear whether cortically-constrained distributed source models will necessarily perform better (Zumsteg and Wennberg, 2005).

In this study we apply a variety of EEG source localization techniques to the same K-complexes recorded in the same 6 patients with epilepsy that were presented in our study defining the intracranial cortical localization of the human K-complex (Wennberg, 2010b). In this way, the true neurophysiologic “forward model” of the EEG waveforms is known. Furthermore, we apply different source localization techniques to K-complexes recorded with MEG in 3 of the patients and to K-complexes recorded with MEG and high density EEG in an additional subject without epilepsy. Specifically, we compare single moving, fixed coherent and multiple dipole models with standardized low-resolution electromagnetic tomography (sLORETA) and low-resolution electromagnetic tomography (LORETA) distributed source modeling, techniques theoretically better suited to modeling extended cortical sources. The goal of the study is to determine whether EEG source imaging (ESI) or magnetic source imaging (MSI) can model human K-complexes in a valid and reliable fashion.

6.2. Methods

6.2.1. EEG: subjects and recordings

EEG source localization was performed on the data acquired from six patients (patients 1-6) with medically-refractory epilepsy during their routine pre-surgical stereoelectroencephalographic recordings. This is the same data set of simultaneously acquired intracranial and scalp EEG used to determine the intracranial localization of the K-complex
(Wennberg, 2010b). Details of the patients’ epilepsies, neuroimaging and anti-epileptic medications have been presented previously (Wennberg, 2010b). All patients gave informed consent and studies were approved by the institutional research ethics board. One of the authors (RW) served as an additional subject (subject 7) for a high density EEG recording using 87 scalp electrodes, manually applied at the 85 positions of the International 10-10 system (Oostenveld and Praamstra, 2001) plus zygomatic (surface sphenoidal) electrodes Sp1/2.

In patients, recordings were carried out using 27 (patients 1-5) or 21 (patient 6) scalp EEG electrodes, placed according to the International 10-20 system plus zygomatics (Sp1/2) and, in patients 1-5, additional F9/10, T9/10 and P9/10 electrodes. As described previously, simultaneous intracranial macroelectrode recordings were obtained in the six patients from stereotactically implanted subdural strip or depth electrodes (Wennberg, 2010b). The acquisition reference electrode and ground were situated near CPz and FCz. Recordings were acquired using a digital EEG system (XLTEK, Oakville, ON, Canada) and a sampling frequency of 200 or 500 Hz.

K-complexes were visually identified in stage 2 sleep during the first or second night of patients’ clinical recordings, and during a single 4-hour recording in subject 7, using standard electrographic criteria (Rechtschaffen and Kales, 1968). Artifact-free samples were archived for off-line analysis. K-complex waveforms were averaged (35-50 per subject) on the extreme value of the scalp EEG channel with maximal amplitude in referential (common average) montage at the major surface-negative peak (usually Fz, occasionally F3 or F4, rarely Fp1 or Fp2) using Insight software (Persyst, Prescott, AZ, USA).

Unless stated otherwise, raw EEG recordings of individual or averaged K-complexes have been digitally reformatted for figure presentation in common average reference montages as in (Wennberg, 2010b), the common average reference comprising the following twelve scalp electrodes: T3, T5, F3, C3, P3, O1, F4, C4, P4, O2, T4, T6.
6.2.2. EEG: source localization

Source localization of independent and averaged K-complexes was performed using CURRY 6 (Abbotsford, Victoria, Australia). CURRY is a commercially available multi-modal software package that implements several source localization models within one platform, facilitating direct comparison of results obtained using different models applied to the same data (Plummer et al., 2007, 2010a,b; Wang et al., 2011).

For this study, epochs containing K-complexes were generated using a time window from -1500 to +500 ms relative to the main negative peak. The interval selected for source localization analysis was marked from onset to peak latency of the main negative wave using a butterfly plot and common average reference of all electrodes. Noise level was estimated as the variance of the data in the signal from -1500 to -500 ms before each individual or averaged K-complex. Electrode positions were registered through label-matching within CURRY 6. The bandpass filter for source localization was 1-30 Hz.

6.2.3. Data preprocessing

The effects on source localization of preprocessing the averaged K-complex data using principal component analysis (PCA) and independent component analysis (ICA) were analyzed. In this de-noising procedure, PCA was first performed on the data to identify orthogonal (uncorrelated) components, which then underwent ICA to identify statistically independent signal components. Mean global field orthogonal signal components of K-complexes with a signal to noise ratio (SNR) > 1.0 identified by PCA underwent ICA (Onton et al., 2006; Plummer et al., 2007, 2010a,b).

6.2.4. Number of electrodes
To assess the effects of different numbers of scalp electrodes (Lantz et al., 2003; Michel et al., 2004) on source localization results, solutions for the same K-complexes were compared using subsets of 19, 21, 27 or 87 electrode sites.

6.2.5. EEG: forward models

The effects on EEG source localization of different forward models (volume conductors; Fuchs et al., 2001, 2007) were assessed in patients by comparing localization results obtained using two different realistic volume conductors: (a) an individualized model created from a patient’s own MRI using the boundary element method (BEM), or (b) a generic model created from the Montreal Neurological Institute (MNI) averaged MRI dataset using the finite element interpolated method (FEMi). Both types of models were created within the CURRY 6 software platform.

6.2.6. EEG: inverse models

Dipole mapping was performed using a single moving dipole model algorithm and a fixed coherent dipole (FCD) modeling algorithm, the latter corresponding to the classical equivalent current dipole model. Single and multiple dipole models were assessed using the FCD algorithm. The effects of regularization on the dipole modeling algorithms were assessed, using a weighting (regularization parameter) of $\lambda = 1.0$ (eliminating dipole components with a contribution to the forward-fit signal $< 1.0$ of the SNR at a given time point; Michel et al., 2004; Plummer et al., 2007, 2010a,b). In the moving dipole algorithm, solutions obtained at the negative peak of the K-complex were compared with those obtained at the midpoint of the negative wave upswing. Confidence ellipsoids (CEs) surrounding dipole solutions indicate regions within which changes in forward calculated data would be below noise compared to the forward calculated data obtained for the best-fit dipole location (Fuchs et al., 2004).
Distributed source modeling was performed using sLORETA (Pascual-Marqui, 2002; Wagner et al., 2004). sLORETA results were compared, in some instances, with results obtained on the same data using LORETA (Pascual-Marqui et al., 1994; Pasqual-Marqui, 1999). The effects on localization of solution space choices were analyzed by comparing results obtained with: (a) a whole brain volume (no cortical constraint) 3D grid, (b) a cortically constrained subspace with rotating sources, (c) a cortically constrained subspace with fixed sources normal to cortex, and (d) a cortically constrained subspace with fixed sources extended over a 20 mm patch or a 100 mm patch (Plummer et al., 2010a,b). Results are depicted in figures overlying either the patients’ own MRIs or a high-resolution cortex segmentation of the MNI averaged MRI dataset. The cutoff threshold for display of distributed source solutions was set at 50%: solutions with smaller explained field percentages (as a percentage of the largest current) were excluded from display.

6.2.7. MEG: subjects and recordings

K-complexes were recorded with MEG during stage 2 sleep in patients 2 (n = 67), 4 (n = 14) and 5 (n = 37), and in subject 7 (n = 55). Patient 1 also underwent MEG as part of routine pre-surgical investigation, but sleep did not occur during the recording. MEG and simultaneous EEG was recorded using a 151-channel whole head CTF MEG system (Port Coquitlam, BC, Canada) and 19 standard 10-20 scalp EEG channels. Fifteen separate 2-min recording segments were obtained. Sampling rate was 625 Hz.

6.2.8. MEG: source localization

Source localization of averaged K-complexes was performed using CURRY 6 as described for EEG. K-complexes were epoched from -1500 to +500 ms relative to the main negative EEG peak. The interval selected for source localization analysis was marked from onset to peak latency of the main negative EEG wave. MEG noise level was estimated as the variance
of the data in the signal from -1500 to -500 ms before the averaged K-complex. The bandpass filter for source localization was 1-30 Hz.

6.2.9. MEG: forward models

The effects on MEG source localization of different volume conductors were assessed in patients by comparing localization results obtained using either: (a) a spherical model calculated from the MNI averaged brain MRI dataset, or (b) an individualized model created from a patient’s own MRI using the boundary element method (BEM).

6.2.10. MEG: inverse models

Single and multiple dipole mapping were performed using the FCD algorithm. Distributed source modeling was performed using sLORETA and the different solution subspace constraints described for EEG source localization.

6.3. Results

6.3.1. EEG: dipole mapping

Fig. 6.2 shows the results of FCD mapping in patients 1-6. Localization results were essentially identical whether the generic FEMi volume conductor or the patients’ own BEM volume conductors were used as the forward model. In all cases deep interhemispheric dipole solutions were provided to explain the large mid frontal maximum electric field. Comparison with the known intracranial superficial frontal cortical source (Fig. 6.1; Wennberg, 2010b) reveals that these dipole source localizations are not physiologically valid.

The addition of the extra subtemporal electrodes to the standard 19 10-20 electrodes deepened the dipole source solution in patients 2, 3, 4 and 6 but had little effect in patients 1 and 5.
The explained variance ($V$) of the best-fit dipole solution (point of minimum residual deviation, RD; $V = 1 - RD^2$) was above 94% in each case and the corresponding CEs were small. Supplementary Table 6.S1 presents the quantitative values of the best-fit FCD parameters for each patient, including dipole amplitude, latency, SNR, three-dimensional dipole localization coordinates and dipole orientation vectors.

Fig. 6.3 shows the results of source localization using the moving dipole algorithm in patients 1-6. Deep interhemispheric solutions were obtained in all patients, similar to those obtained using the FCD algorithm (Fig. 6.2). Best-fit solutions were deeper near the peak of the negative wave than at the midpoint of the wave upswing in patient 3. Peak versus mid upswing source localizations differed minimally in the other patients. CE volumes were much larger at midpoint versus peak (Fig. 6.3).

Fig. 6.4 shows the deep interhemispheric solutions obtained using both inverse models in subject 7, as calculated from 19, 21 and 87 scalp electrodes. Addition of the subtemporal zygomatic electrodes to the standard 19 10-20 electrodes deepened the source solutions slightly (similar to patients 2, 3, 4 and 6, Fig. 6.2) whereas inclusion of all 87 scalp electrodes in the calculations resulted in solutions slightly more superior and posterior, though the differences were minor.

Supplementary Fig. 6.S1 shows the effects of preprocessing the data with PCA (2 components) and ICA, as well as the effects of regularization upon the source localization results obtained using the single moving dipole and FCD algorithms in subject 7. Neither preprocessing nor dipole component regularization altered localization of the deep midline source solutions. Preprocessing with PCA/ICA and application of regularization to both inverse dipole mapping models likewise showed minimal effects in patients 1-6 (data not shown).

Supplementary Fig. 6.S2 shows the results of FCD mapping using two dipole fit sources in subject 7, with the dipoles either unconstrained (Supplementary Fig. 6.S2A) or constrained to mirrored locations along the mid sagittal plane (Supplementary Fig. 6.S2B). Regularization of the
multiple dipole models did lead to some changes in source solutions, most evident as an inferior shift of the mirrored source locations from bilateral caudate nuclei to inferior frontal gyri, as well as decreased CE volumes. However, regularization did not improve the validity of the source localization results, and deep midline solutions were returned in all of the two dipole fit models.

6.3.2. Propagation

Examination of the orientation of the moving dipole solutions in patients 1-6 did not suggest propagation of the negative K-complex component as a traveling wave (Fig. 6.3). In subject 7, localization of the moving dipole solutions over time evolved gradually from a more anterior/inferior to a more posterior/superior location, however, dipole orientation did not change (Fig. 6.4, Supplementary Fig. 6.S1).

Propagation was further assessed by examination of: (a) temporal changes in voltage topographic plots during the upswing of the negative K-complex wave and (b) the timing of wave onset and peak latencies at different electrode sites across the scalp (Supplementary Figs. 6.S3-6.S5). Results from these investigations are presented in the Supplementary material. None of the analysis techniques provided definitive evidence for or against wave propagation versus superimposition of sources.

6.3.3. EEG: distributed source modeling

Fig. 6.5 shows the results of distributed source modeling with sLORETA in patients 1-6. Localization results were similar using different forward models and solution spaces, in this case either the generic FEMi volume conductor and cortical patch subspace constraint or the patients’ own BEM volume conductors and a non-constrained 3D grid solution space. In all cases maximal current density source solutions were localized to deep midline regions (subcallosal gyrus in patients 1, 5 and 6, inferior temporal gyrus in patient 2, corpus callosum in patient 3, lentiform
nucleus in patient 4), and not to the superficial frontal cortical regions physiologically responsible for generation of the K-complex.

\( V \) of the best-fit sLORETA solution (point of minimum RD) was above 98% in each case. Supplementary Table 6.S2 presents the quantitative values of the best-fit sLORETA parameters for each patient, including current density reconstruction (CDR) F-distribution, latency, SNR, three-dimensional CDR dipole localization coordinates and orientation vectors.

Fig. 6.6 shows the effects of the different subspace solution constraints on sLORETA modeling of K-complexes recorded in subject 7. Choice of solution space did affect the extent and continuity of the distributed source solutions, however, similar deep midline source maxima were found with all of the different solution spaces.

A comparison of sLORETA localization results with those obtained using the LORETA inverse model (which, unlike moving dipole, FCD and sLORETA algorithms, is not based on minimum norm estimation) showed qualitatively similar source solutions in all subjects. As with the other inverse models tested, LORETA provided deep source maxima localized to brain regions uninvolved in K-complex generation; examples from subject 7 are shown in Fig. 6.7.

The maximal localization of the distributed source solutions differed little between modeling at the mid upswing of the negative wave and modeling at the K-complex peak (although \( V \) was slightly greater and SNR much higher when modeling was performed at the peak of the negative wave; Fig. 6.7).

6.3.4. Reliability

Similar results obtained in all 7 subjects suggest high reliability of the different source localization techniques as applied to averaged K-complexes. Source localization using the same techniques was also performed on individual K-complexes in subject 7 for comparison with the averaged waveform results. The localization results obtained with dipole mapping using the FCD algorithm and distributed source modeling using sLORETA are shown in Fig. 6.8.
Table 6.1 presents the best-fit FCD source parameters for individual and averaged K-complexes in subject 7. CE volumes were larger and SNR values were lower for the individual K-complexes but source localization coordinates and $V$ values were comparable to the results obtained for the averaged potential. Table 6.2 presents the quantitative values of the best-fit sLORETA parameters obtained with modeling of the same data. SNR was larger and $V$ marginally increased in calculations performed on the averaged, as compared to the individual, K-complexes, but all reliably returned similar deep midline source localization solutions.

6.3.5. MEG: dipole mapping

The results of FCD mapping of averaged K-complexes recorded with MEG in patients 2, 4 and 5 are shown in Supplementary Fig. 6.S6. Deep interhemispheric single dipole source solutions were obtained in all three patients using both the generic sphere forward model and the patients’ own BEM volume conductors. $V$ values ranged from a low of 56% (patient 5, sphere) to a high of 92% (patient 4, sphere). Neither PCA/ICA data preprocessing nor regularization applied to the FCD algorithm improved localization results (data not shown). Unlike the uniform EEG surface topographic voltage plots recorded in all subjects, surface topographic maps of K-complex magnetic fields were not uniform across subjects (Supplementary Fig. 6.S6). The most well-developed symmetrical magnetic field map was that obtained in patient 2, who had the most MEG K-complexes available ($n = 67$) for averaging. A somewhat similar field map was apparent in subject 7, who had 55 MEG K-complexes available for averaging (Supplementary Fig. 6.S7). In contrast, magnetic field maps in patients 4 and 5 were different, despite identical mid frontal electric field maxima (not shown), presumably related to the lesser number of MEG K-complexes available for averaging in these patients ($n = 14$ and $n = 37$) and the fact that the MEG K-complex waveform is of much lower amplitude relative to baseline than the corresponding EEG potential.

Dipole mapping using multiple dipoles and the FCD algorithm increased $V$ to 90% or above in all patients but did not improve upon the physiological validity of localization results.
Fig. 6.9 shows the results of multiple dipole mapping in patient 2 with one, two or three dipoles, and the corresponding increase in $V$ from 83% to 88% to 98% ($V$ decreased to 91% with the addition of a fourth dipole). In this case, localization of the different MEG dipole solutions corresponded predictably to the topographic magnetic fields, with sources situated deep to the different dipolar field arrangements, the final solutions constrained by the choice of dipole number in the inverse model (in the same way a single deep dipole solution is predictably provided by the inverse models to explain the topographic electric field of the EEG K-complex).

6.3.6. MEG: distributed source modeling

Fig. 6.10 shows the results of MEG distributed source modeling using sLORETA in patients 2, 4 and 5. Localization results were similar using different forward models (generic sphere or patients’ own BEM volume conductors) and solution spaces (whole volume 3D grid or cortically constrained patch). In each case maximal CDR source solutions were localized to regions far removed from the superficial frontal cortices responsible for generation of the K-complex electric field (corpus callosum in patient 2 ($V = 91\%$, SNR = 5.2), inferior parietal lobule in patient 5 ($V = 78\%$, SNR = 3.8), deep extranuclear midline structures in patient 4 ($V = 90\%$, SNR = 5.2)).

Supplementary Fig. 6.S7 shows the effects of the four different subspace solution constraints on results obtained from sLORETA modeling of the averaged MEG K-complexes recorded in subject 7. Physiologically valid source localizations were not obtained with any of the different solution spaces.

6.4. Discussion

This study sought to determine whether source localization techniques that are currently used to describe the underlying generators of sensory, motor or cognitive brain responses in humans could also be used to model human K-complexes in a valid and reliable fashion. The K-
complex was selected for study for two reasons: (a) burgeoning research interest in sleep neurophysiology would benefit from being able to noninvasively model the K-complex with ESI or MSI techniques, and (b) as the largest surface recorded potential in the normal human EEG, the K-complex provides an ideal tool by which to assess the utility of ESI and MSI as applied to large, synchronous superficial cortical sources, such as may be associated not only with the K-complex, but also with sleep slow waves and widespread epileptiform discharges, e.g., generalized spike/wave complexes.

The study is unique in that we were able to compare noninvasive ESI and MSI results directly to the intracranial EEG field recordings in the same patients previously described in a study of the cortical localization of the human K-complex (Wennberg, 2010b). This provided unambiguous information regarding the true intracranial activity associated with these patients’ K-complexes (a large electrical field widely distributed across the anterior and superior frontal cortices) with which we could validate the noninvasive source localization techniques. The aim of the study was to determine whether any combination of modern source localization forward and inverse modeling methods, as applied to EEG and MEG data, would be able to provide an accurate depiction of the intracranial generator of the K-complex. The ability to accurately model the K-complex noninvasively with ESI or MSI would be extremely useful in a number of clinical and basic research applications. However, if noninvasive ESI or MSI techniques provide falsely localizing solutions, use of the techniques for clinical or research purposes could be misleading and counterproductive.

6.4.1. EEG

We found ESI of K-complexes to be highly reliable but, unfortunately, not physiologically valid. Source localization solutions returned by different dipole mapping or distributed source modeling algorithms were invariably falsely localized to deep interhemispheric structures. Choice of realistic forward model, between a generic FEMi volume conductor and an
individualized BEM volume conductor created from a subject’s own MRI, had little effect on localization results. Although we expected that single dipole mapping approaches would be prone to such incorrect solutions, surprisingly distributed source modeling, a technique hypothetically more attractive than single dipole mapping given the known distribution of the electrical generating source across an extended area of cortex, returned similar deep physiologically invalid solutions as were provided with dipole mapping. Different choices of more or less realistic solution spaces for distributed modeling did not improve the validity of localization results.

Our findings provide further evidence of the propensity of source localization algorithms to provide deep interhemispheric solutions for signals generated by large synchronous cortical sources (Nunez, 1990; Romani and Pizzella, 1990; Hämäläinen et al., 1993; Numminen et al., 1996; Kobayashi et al., 2005; Zumsteg and Wennberg, 2005), and distributed modeling appears to offer no advantage over dipole mapping in this regard. These findings have implications beyond the study of K-complexes as similar deep interhemispheric localization solutions are likely when modeling other large synchronous sources such as sleep slow waves (Murphy et al., 2009) and generalized spike/wave complexes in epilepsy (Rodin et al., 1994; Holmes et al., 2004; Zumsteg and Wennberg, 2005).

A number of methods for improving accuracy and/or stabilizing the source solutions were investigated. Data preprocessing with PCA and ICA did not alter localization results and the validity of dipole mapping results was not improved by the application of regularization to the inverse models. Variation in the number of EEG electrodes used in the source modeling calculations (from 19 to 87) did not materially affect the ESI localization results. It must be acknowledged, however, that the high density 87-channel EEG recording did not include electrodes placed below the zygomatic line. It is possible that the addition of more inferiorly placed electrodes on the face and neck could shift K-complex source localizations superiorly, though this is an untested hypothesis. The deep interhemispheric source localizations of sleep slow waves and generalized spike/wave discharges obtained with ESI of 256-channel high
density recordings (Holmes et al., 2004; Murphy et al., 2009) suggests that the effects of additional inferior electrodes in this regard may be minimal.

Though not a major focus of this study, the possibility that K-complexes represent propagated traveling waves (Massimini et al., 2004) was explored through examination of changes in moving dipole source orientation, differences between the localization of sources modeled at the midpoint of the negative wave upswing and sources modeled at the negative peak, examination of the raw EEG waveforms of individual K-complexes recorded with high density EEG and the spatiotemporal changes in surface voltage topography of averaged K-complexes. As with analysis of intracranial EEG recordings of K-complexes (Wennberg, 2010b), definitive evidence of K-complex propagation as a traveling wave could not be identified. Nonetheless, in some subjects, at least some K-complexes did show earlier wave onsets or peaks over frontal polar as compared with mid frontal regions. Whether this represents propagation of the negative wave in these instances or superimposition of separate sources has not yet been determined. In any event, for source localization purposes, ESI of both early and late components of the K-complex negative wave produced physiologically invalid deep midline frontal sources shifting from the orbitofrontal to anterior cingulate regions, all far removed from the superficial frontal cortical generators of the intracranially recorded K-complex.

Although solutions were not physiologically valid, ESI of K-complexes was very consistent across individual and averaged potentials, both within and across subjects, indicating that failures of source modeling could not be simply attributed to spurious fits due to random noise or artifacts. Source solutions were highly comparable across all 7 subjects and solutions for individual K-complexes differed little from solutions for averaged K-complexes. The reliability of ESI in this setting is presumably related to the high SNR associated with this large amplitude potential.

6.4.2. MEG
MSI of K-complexes did not provide physiologically valid results and source localization of MEG K-complexes was less reliable than ESI. Individual K-complex magnetic fields recorded with MEG are of much lower amplitude relative to baseline than the corresponding electric fields recorded with EEG. This is presumably due to a combination of: (a) greater cancellation effects of extended fields recorded with MEG as compared to EEG, and (b) relative insensitivity to radially oriented sources in MEG as compared to EEG (Ahlfors et al., 2010a,b). It is interesting to note that similar observations have been made for the early component of pre-movement brain activity, assumed to arise from bilateral activation of the supplementary motor areas in the medial frontal cortices, which is more robustly measured with EEG as compared to MEG, also presumably due to a combination of source orientation effects and cancellation of opposing currents in the medial frontal cortices (Lang et al., 1991; Erdler et al., 2000). In the current study, averaging of multiple K-complexes (i.e., more than 50) was required before a stable symmetrical topographic field map could be appreciated, and even after averaging this many MEG K-complexes the SNR for source localization was only approximately one fifth that of averaged EEG K-complexes. This relative disparity in SNR between MEG and EEG is presumably the major contributor to the differences in reliability between MSI and ESI of K-complexes.

Single dipole mapping returned deep interhemispheric source solutions in all cases. Multiple dipole mapping increased $V$ but did not result in solutions of increased physiologic validity. Distributed source modeling provided no further improvement, irrespective of choice of volume conductor or solution space.

In conclusion, neither ESI nor MSI performed with currently available source localization techniques was able to provide physiologically valid noninvasive source localization of the human K-complex. ESI was more reliable than MSI, but reliability of a method is of limited importance if its results are not valid. It was hoped that the intuitively more appealing distributed source modeling techniques would outperform dipole mapping in localizing the large distributed
cortical source of the K-complex. However, we did not find distributed source modeling results
that were physiologically valid, and the interhemispheric preponderance of noninvasive ESI and
MSI, when confronted with widespread and symmetrical electric and magnetic fields, seems to
apply equally to both distributed source modeling and dipole mapping (Zumsteg and Wennberg,
2005).

Future developments are needed to enable accurate noninvasive source localization of
large synchronous superficial cortical fields with ESI or MSI. New inverse models are constantly
being developed and these will need to be tested in their turn. Improvements in realistic forward
models that better model extended cortical patches across gyral and sulcal surfaces might
theoretically improve localization accuracy and prevent the propensity for deep localization of
extended cortical sources. Improved cortical segmentation algorithms for construction of high
resolution gyral and sulcal solution spaces might also theoretically improve the validity of
distributed source modeling results. Until such developments are realized, however, noninvasive
source localization cannot be used to study sleep K-complexes without much circumspection, and
similar caution is required when interpreting ESI and MSI of any large symmetrical synchronous
field.
Table 6.1. Best-fit FCD parameters for 5 individual K-complexes and averaged K-complex, EEG, subject 7

<table>
<thead>
<tr>
<th>KC</th>
<th>Elec</th>
<th>Lat (ms)</th>
<th>Amp (μAmm)</th>
<th>CE (ml)</th>
<th>V (%)</th>
<th>RD (%)</th>
<th>SNR</th>
<th>x (mm)</th>
<th>y (mm)</th>
<th>z (mm)</th>
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<th>ny</th>
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FEM Volume Conductor, 3D Grid

1 Medial Frontal Gyrus, BA 25
2 Medial Frontal Gyrus, BA 25
3 Interhemispheric Frontal
4 Medial Frontal Gyrus, BA 11
5 Anterior Cingulate

AV=averaged (n=50) K-complex, Elec=electrodes, Lat=latency, Amp=amplitude, CE=confidence ellipsoid, V=variance, RD=residual deviation, SNR=signal to noise ratio, x=right +ve left – ve axis, y=anterior +ve posterior –ve axis, z=superior +ve inferior –ve axis, nx=leftward +ve rightward –ve dipole orientation (vector fraction of 1.0), ny=backward +ve forward –ve dipole orientation (vector fraction of 1.0), nz=downward +ve upward –ve dipole orientation (vector fraction of 1.0).
Table 6.2. Best-fit sLORETA parameters for 5 individual K-complexes and averaged K-complex, EEG, subject 7

<table>
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<tr>
<th>K C</th>
<th>Elec (##)</th>
<th>Lat (ms)</th>
<th>CDR F-dist</th>
<th>FWHM (m)</th>
<th>V (%)</th>
<th>RD (%)</th>
<th>SNR</th>
<th>x (mm)</th>
<th>y (mm)</th>
<th>z (mm)</th>
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FEM Volume Conductor, Cortical Surface Patch

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<td>A</td>
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KC=K-complex, AV=averaged (n=50) K-complex, Elec=electrodes, Lat=latency, CDR F-dist=current density reconstruction F-distribution, λ=regularization value, FWHM=full-width half maximum, V=variance, RD=residual deviation, SNR=signal to noise ratio, x=right +ve left –ve axis, y=anterior +ve posterior –ve axis, z=superior +ve inferior –ve axis, nx=leftward +ve rightward –ve CDR dipole orientation (vector fraction of 1.0), ny=backward +ve forward –ve CDR dipole orientation (vector fraction of 1.0), nz=downward +ve upward –ve CDR dipole orientation (vector fraction of 1.0).
Fig. 6.1. Composite diagram of averaged EEG K-complex waveforms recorded in patients from scalp, frontal lobe cortex, frontal lobe white matter, thalamus, and medial occipital lobe. Surface negative scalp EEG peak maximal at Fz > F3,4 > Cz corresponds to synchronous surface negative intracranial peak recorded with widespread bilateral frontal lobe cortical distribution. Inverted (positive polarity) waveforms recorded synchronously from intracranial electrode contacts situated in frontal white matter, thalamus and medial occipital region and from occipital scalp electrode (O2). Waveforms plotted for illustrative purposes on 3D rendering of MNI averaged MRI dataset. MRI insets show locations of patients’ intracranial subdural and depth electrodes. Scalp and intracranial EEG depicted in common average (12 scalp electrodes) referential montage; LFF = 0.5 Hz; HFF = 70 Hz. (Adapted from Figs. 1, 4, 6-9 in Wennberg, 2010b).
Fig. 6.2. Scalp EEG voltage topographic maps and dipole source localizations of averaged K-complexes recorded in patients 1-6, arranged in order from left (patient 1) to right (patient 6). Top. Scalp voltage topographic maps at K-complex surface negative peak; 27 scalp EEG electrodes (patients 1-5), 21 scalp EEG electrodes (patient 6). Middle. Fixed coherent dipole (FCD) source localizations (surrounded by their confidence ellipsoid (CE) volumes) obtained using EEG data from 19 electrodes (standard 10-20, blue), 21 electrodes (10-20 plus zygomatics, patients 1-5, green, patient 6, red) and 27 electrodes (10-20 plus zygomatics, F9/10, T9/10, P9/10, patients 1-5, red). Volume conductor for each patient = BEM created from patient’s own MRI; results plotted on patient’s MRI. Bottom. Dipole source localizations obtained using the same EEG data and inverse model but using an alternate non-individualized forward model, the FEMi volume conductor created from the MNI averaged brain MRI dataset. Both forward models were associated with similar deep midline source solutions.
**Fig. 6.3.** Moving dipole source localizations of averaged K-complexes in patients 1-6; same EEG data used for FCD mapping in Fig. 6.2. Volume conductor = FEMi. EEG butterfly plots: common average reference, negative up, this and all other figures. MGFP = mean global field power. For each patient, results plotted above baseline show moving dipole trajectory over time period analyzed from initial negative upswing to just after maximal negative peak of K-complex; size of dipole marker corresponds to dipole strength at each time point. Results plotted below each patient’s baseline represent single moving dipole solutions, surrounded by their CEs, plotted at the midpoint of the negative upswing (determined as the timepoint: ½ x maximum MGFP value, with values between -48 and -60 ms). Solutions were similar to those obtained using the FCD inverse model (Fig. 6.2); dipole strengths were lower (and CEs larger) at the midpoint of negative upswings compared with solutions closer to negative peaks.
Fig. 6.4. Moving and FCD source localizations of averaged K-complexes (n=50) recorded with 87 scalp EEG electrodes in subject 7. Volume conductor = FEMi. Source localization results (plus corresponding EEG butterfly plots and topographic maps) are shown for 19 electrodes (standard 10-20), 21 electrodes (standard 10-20 plus zygomatics) and 87 electrodes (extended 10-10). Similar deep midline source solutions were found with both inverse models regardless the number of electrodes.
Figure 6.5
Fig. 6.5. Distributed source modeling of averaged K-complexes using sLORETA in patients 1 (top) through 6 (bottom). Same EEG data used for dipole mapping in Figs. 6.2, 6.3 (27 electrodes, patients 1-5, 21 electrodes, patient 6). Shown for each patient are the localization results obtained using (A) the FEMi volume conductor and a cortical subspace constraint comprised of fixed normal sources in a 20 mm extended patch and (B) the patient’s own BEM volume conductor and a whole volume 3D grid subspace. The different forward models and subspace constraints were associated with deep midline source solutions in all patients.
Figure 6.6
Fig. 6.6. Effects of different subspace constraints on sLORETA source localization of averaged K-complexes (n=50) recorded with 87 EEG electrodes in subject 7. From top to bottom, solution subspace = whole volume 3D grid, cortex with rotating sources, cortex with fixed sources normal to cortex, cortex with fixed extended sources over a 20 mm patch, and cortex with fixed extended sources over a 100 mm patch. Volume conductor = FEMi. Although the extent and continuity of the distributed source solution were affected by the choice of subspace constraint, localization maxima were invariably situated in deep interhemispheric regions.
Figure 6.7

Fig. 6.7. Comparison of results obtained using two different distributed source inverse models, sLORETA (left) and LORETA (right). Source localization of averaged K-complexes (n=50) recorded with 27 EEG electrodes (10-20 plus zygomatics, F9/10, T9/10, P9/10) in subject 7. Volume conductor = FEMi. (A) Modeling performed at peak of negative wave (SNR = 27.1). Top row, solution subspace = whole volume 3D grid. Bottom row, solution subspace = cortex with fixed extended sources over a 20 mm patch. All $V > 99\%$. (B) Modeling performed at mid upswing of negative wave (SNR = 16.5). Top row, solution subspace = whole volume 3D grid (sLORETA $V = 97.91\%$, LORETA $V = 99.88\%$). Bottom row, solution subspace = cortex with fixed extended sources over a 20 mm patch (sLORETA $V = 98.21\%$, LORETA $V = 95.42\%$). Localization results were qualitatively similar using both methods.
Fig. 6.8. Reliability of EEG source localization performed on individual K-complexes. Shown are five different K-complexes recorded in subject 7. FCD mapping and sLORETA distributed source modeling performed on the 87 electrode recordings reliably returned deep midline source solutions around the anterior cingulum and corpus callosum. Volume conductor = FEMi. sLORETA solution subspace = cortical constraint, fixed normal sources, 20 mm extended patch.
Fig. 6.9. Results of multiple dipole mapping of averaged MEG K-complexes (n=67) in patient 2. (A) Butterfly plot of simultaneous EEG (blue) and MEG (green) averaged K-complex waveforms. (B) EEG/MEG topographic waveform plots and field maps at K-complex peak. (C) Localization of single dipole solution (cingulate gyrus, top), two dipole solution (cingulate gyrus and precuneus, middle) and three dipole solution (bilateral temporal lobes and deep midline occipital region, bottom). Forward model = sphere volume conductor. Inverse model = FCD. Explained variance ($V$) increased with addition of second and third dipoles to model recorded magnetic fields but dipole source localizations became less valid physiologically.
Figure 6.10

Fig. 6.10. Distributed source modeling of averaged MEG K-complexes using sLORETA in patients 2 (top), 5 (middle) and 4 (bottom). Same MEG data used for dipole mapping in Supplementary Fig. 6.S6. (A) Forward model = patient’s own BEM volume conductor. Subspace constraint = whole volume 3D grid. (B) Forward model = sphere volume conductor calculated from MNI averaged brain MRI dataset. Subspace constraint = whole volume 3D grid. (C) Forward model = same sphere volume conductor as in (B). Subspace constraint = cortex, fixed normal sources, 20 mm extended patch. The different forward models and subspace constraints were all associated with physiologically invalid sources.
SUPPLEMENTARY DATA TO: ON NONINVASIVE SOURCE IMAGING OF THE HUMAN K-COMPLEX

K-COMPLEX PROPAGATION

VOLTAGE TOPOGRAPHY

Inspection of a series of continuous surface voltage topographic plots during the upswing of the negative K-complex wave in subject 7 revealed early maximal frontal polar negativity, later evolving into a more superior mid frontal maximum at the negative peak (Supplementary Fig. 6.S3A). Following the peak maximum, surface negativity receded during the downswing of the negative wave with no change in the mid frontal maximal localization (not shown).

Similar temporal shifts in surface voltage topography from frontal polar to mid frontal maxima during the negative wave upswing were identified in patient 2 (Supplementary Fig. 6.S3B) and patient 6 (Supplementary Fig. 6.S3C). There were no anterior-posterior spatiotemporal changes in surface voltage topographic maxima during the negative K-complex wave in the other four patients (not shown).

The combination of the moving dipole orientation results (Figs. 6.3, 6.4, Supplementary Fig. 6.S1) and the temporal topographic plots did not allow for definitive interpretation with respect to wave propagation versus superimposition of earlier (e.g., orbitofrontal) and later (e.g., superior frontal) sources.

INDIVIDUAL AND AVERAGED WAVEFORMS

Supplementary Fig. 6.S4 shows 16 individual K-complexes selected from the 50 events recorded in subject 7. Only some of the individual K-complexes show time lags in either negative wave onsets or negative wave peaks. Most of the individual K-complexes show no clearly discernible evidence of propagation.

Supplementary Fig. 6.S5 shows the effects of reference electrode choice on the averaged K-complex (n=50) waveform recorded in subject 7. Reformatting to a “monopolar” Oz

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minimizes the frontal polar to mid frontal peak latency by excluding from the reference anterior
electrode positions situated within the negative field of the K-complex peak. However, evidence
persists of a time lag between frontal polar and mid frontal wave onsets in the Oz referential
montage, presumably reflecting inclusion in the averaged waveform of individual K-complexes
with wave onset latencies, such as those in Supplementary Fig. 6.S4B.
Supplementary Figure 6.S1

Fig. 6.S1. Effects of dipole component regularization and EEG data preprocessing with principal and independent component analysis (PCA/ICA) on moving and FCD source localizations of averaged K-complexes (n=50) in subject 7. Volume conductor = FEMi. Source localization results are shown for 19 electrodes (left), 21 electrodes (middle) and 87 electrodes (right). Neither regularization nor PCA/ICA altered localizations of deep midline source solutions found with both inverse models.
Fig. 6.S2. FCD source localizations, using two dipole fit sources, of averaged K-complexes (n=50) recorded with 87 electrodes in subject 7. (A) Solutions obtained using two unconstrained dipole sources, with and without regularization. (B) Solutions obtained using two dipole sources constrained to mirrored locations along the sagittal midline, with and without regularization. Regularization shifted inferiorly the mirrored source locations from bilateral caudate nuclei to inferior frontal gyri, and decreased CEs. Deep midline source solutions were found with the constrained and unconstrained models.
Supplementary Figure 6.S3B
Fig. 6.S3. (A) Propagation of surface voltage topographic maps during rise of averaged (n=50) K-complex negative wave from -218 ms to peak at 0 ms in subject 7, 87 electrode scalp EEG recording. Earliest negativity develops over frontal polar region (Fpz, Fp1/2) during initial 150 ms, then becomes maximal over anterior frontal midline (AFz, AF1/2) over next 25 ms, before extending posteriorly to its final stable peak maximum over the anterior-mid frontal region (AFz, Fz, AF1/2, F1/2). (B) Propagation of surface voltage topographic maps during rise of averaged (n=50) K-complex negative wave from -218 ms to peak at 0 ms in patient 2, 27 electrode scalp EEG recording. Earliest negativity involves frontal polar region (Fp1/2) to an extent approximately equal to mid frontal (Fz) involvement during initial 130 ms, before developing more restricted mid frontal stable peak maximum. (C) Propagation of surface voltage topographic maps during rise of averaged (n=35) K-complex negative wave from -220 ms to peak at 0 ms in patient 6, 21 electrode scalp EEG recording. Earliest negativity develops over frontal polar region (Fp1/2) during initial 150 ms, before developing peak amplitude maximum over frontal midline (Fz > F3/4, Cz).
Fig. 6.S4. Individual K-complexes recorded in subject 7. 87 electrode scalp EEG recording, common average reference (12 scalp electrodes). (A) Eight K-complexes showing similar anterior-mid frontal maximum scalp distribution. Fourth, fifth and sixth potentials show lesser involvement of frontal polar region. No definite evidence of waveform propagation (neither onset nor peak) in these 8 potentials. (B) Eight different K-complexes, all with anterior-mid frontal peak amplitude maximum and all with frontal polar involvement. Anterior-posterior time lags apparent at waveform onsets in third, fourth and sixth potentials (red vertical lines) and at waveform peaks in third and fourth potentials. LFF = 0.5 Hz; HFF = 70 Hz.
Supplementary Figure 6.S5

**Fig. 6.S5.** Effects of different reference electrode selections upon averaged K-complex waveform morphologies and peak latencies, subject 7, 87 electrode recording. Left column, common average reference of 17 electrodes (F7, T3, T5, F3, C3, P3, O1, Fz, Cz, Pz, F4, C4, P4, O2, F8, T4, T6); middle column, common average reference of 12 electrodes (T3, T5, F3, C3, P3, O1, F4, C4, P4, O2, T4, T6); right column, midline occipital Oz electrode reference. Exclusion of midline frontal electrodes from common average results in slight change in maximal peak amplitude (larger anterior/superior negative peak, smaller posterior/inferior positive peak) with no appreciable effect on peak latency (compare middle column with left column). Posterior occipital midline “monopolar” referential montage results in increased negative peak amplitude and decreased frontal polar to anterior-mid frontal peak latency. Frontal polar to anterior-mid frontal waveform onset latencies, however, persist in the averaged K-complex after reformatting to the occipital referential montage (red vertical lines, right column).
Supplementary Figure 6.S6

Fig. 6.S6. FCD source localizations (and surrounding CEs) of averaged MEG K-complexes recorded in patients 2 (top, n=67), 5 (middle, n=37) and 4 (bottom, n=14). (A) Forward model = sphere volume conductor calculated from MNI averaged brain MRI dataset. (B) MEG topographic field maps at time of K-complex (EEG negative) peak. (C) Forward model = patient’s own BEM volume conductor. Deep midline dipole solutions in each patient using both forward models.
**Fig. 6.S7.** Effects of different subspace constraints on sLORETA source localization of averaged MEG K-complexes (n=55) recorded in subject 7. From top to bottom, solution subspace = whole volume 3D grid, cortex with rotating sources, cortex with fixed sources normal to cortex, and cortex with fixed extended sources over a 20 mm patch ($V=91\%$, SNR=6.2). Volume conductor = sphere calculated from MNI averaged brain MRI dataset. Bottom row shows butterfly plots of averaged MEG (green) and EEG (blue) data and the corresponding topographic MEG and EEG field maps at time of K-complex (EEG negative) peak. sLORETA did not provide physiologically valid source solutions with any of the different subspace constraints.
Chapter Seven

EEG source imaging of anterior temporal lobe spikes:

Validity and reliability

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Abstract

Objective: To assess the reliability and validity of EEG source localization of anterior temporal lobe spikes through direct comparison with simultaneously recorded intracranial spike fields.

Methods: We recently showed that classical anterior temporal spikes recorded in mesial temporal lobe epilepsy (MTLE) are non-propagated potentials generated in the anterolateral temporal neocortex (Clin. Neurophysiol. 122 (2011) 1295). In this study EEG source imaging (ESI) was performed on 64 identical right anterior temporal spikes (and 48 homologous left anterior temporal spikes) in a patient with MTLE investigated with simultaneous depth and subdural intracranial EEG and 27 channel scalp EEG. The effects of different realistic forward models, low frequency filters (LFFs) and spike averaging were assessed in terms of the reliability and physiologic validity of the source solutions.

Results: Dipole mapping and distributed source modeling solutions for the grand average of all spikes were accurately localized to the superficial anterolateral temporal neocortex within 1 cm of the intracranially defined spike generator, irrespective of forward model or LFF. ESI of single spikes, however, showed poor reliability (i.e., dissimilar localization results for intracranially identical spikes). Even with an optimal combination of individualized volume conductor and 3 Hz LFF more than one third of single spike source solutions were physiologically invalid. Spike averaging, especially of 8 or more spikes, significantly increased the proportion of valid source solutions.

Conclusions: ESI of individual anterior temporal spikes was limited by low reliability and a high likelihood of physiologically invalid source solutions. Spike averaging of 8 or more identical spikes prior to ESI, however, reliably produced accurate source solutions localized to the anterolateral temporal neocortex.

Significance: ESI performed on averages of identical spikes can provide highly accurate noninvasive source localization of the anterolateral temporal neocortical region responsible for
generating classical anterior temporal lobe spikes. The reliability and validity of ESI performed on individual spikes, however, is relatively limited.
7.1. Introduction

Technological advances in recent years have made EEG source imaging (ESI) methods more widely available to end users and it has been suggested that ESI is poised to play an increasing role in the clinical investigation of patients with epilepsy (Plummer et al., 2007, 2008; Brodbeck et al., 2011).

However, before a clinical test is widely implemented it must be demonstrated to be both reliable and valid. A completely reliable investigative technique would provide the same output solution whenever confronted with the same input problem. In epilepsy, the principal role envisaged for ESI in the clinical investigation of patients is to provide noninvasive source localization of interictal spikes. Hence, for ESI to be considered reliable in this role, it must be shown that identical spikes generated in a particular brain region are associated with consistently localized ESI solutions.

Reliability is a necessary component of a good clinical test, however, reliability alone is not enough. To be clinically useful, a test must also be shown to produce data that accurately represent the true (patho)physiological situation in question, i.e., the results provided by the test must be physiologically valid. In the case of ESI in epilepsy, the source solution of an interictal spike must be understood to accurately represent the true intracranial cortical generator of the extracranially-recorded spike field.

To the clinical neurophysiologist investigating a patient, these issues coalesce into one important question: “If I model a number of spikes that appear to me to be essentially identical and presumably arising from the same spot in the brain, will I get an identical, or nearly identical, source solution each time, within a reasonably small area of cortex, at a level of localization better than what I can surmise by simply looking at the raw data?” (i.e., something significantly better than localization at the lobar or gross sublobar level). The last point is important because it is not only reliability and validity that is desired of a new technique such as ESI, but also true added value. It is of little benefit to perform an additional, moderately complex and time
consuming test if the final results are no better than what can be obtained from a quick visual analysis of the data.

There has been surprisingly little research published that addresses the issues of reliability and validity of ESI in the clinical setting. Clinical ESI studies in epilepsy have concentrated primarily on temporal lobe epilepsy and have usually addressed reliability and validity only indirectly (Michel et al., 2004a; Plummer et al., 2008; Brodbeck et al., 2011). Validity has been most commonly assessed by looking for correlations between source localization solutions and surgical outcomes. In the most typical example, spikes localized to the temporal lobe by ESI were presumed to be valid if a patient became seizure free after surgical resection of the anteromesial temporal lobe (Waberski et al., 2000; Huppertz et al., 2001; Michel et al., 2004b; Brodbeck et al., 2011; Wang et al., 2011). However, particularly for mesial temporal lobe epilepsy (MTLE), the spikes most frequently recorded with scalp EEG arise in superficial neocortex situated centimetres away from the mesial temporal structures responsible for seizure onsets, and seizure freedom after anteromesial temporal resection does not depend on removal of the neocortical areas responsible for generation of the scalp-recorded interictal spikes (Cendes et al., 1993; Wennberg et al., 1997a, 2011). Indeed, MTLE patients’ typical anterior temporal neocortical spikes often become more abundant after selective surgical resection of the ipsilateral mesial temporal structures responsible for seizure generation (Niemeyer, 1958; Cendes et al., 1993; Wennberg et al., 1997b). In consideration of these longstanding observations, it has been suggested that assessing the validity of temporal lobe interictal spike source localizations by correlating with surgical outcomes may not be entirely rational (Zumsteg et al., 2005; Plummer et al., 2008; Wennberg et al., 2011).

Other studies have used source localizations of interictal spikes in the vicinity of structural lesions identified by neuroimaging to presume validity of ESI data (Boon et al., 1997; Diekmann et al., 1998; Krings et al., 1998; Worrell et al., 2000; Huppertz et al., 2001; Lantz et al., 2003a; Michel et al., 1999, 2004b). However, it is well known from intracranial EEG
recordings that interictal spikes may be localized at some distance from structural lesions (Talairach and Bancaud, 1966; Zumsteg et al., 2005), such that this method of assessing validity is also less than ideal.

These sorts of analyses (correlations with surgical outcomes and structural lesions) have been interpreted to indicate that ESI has good localization accuracy at the lobar or sublobar level (Lantz et al., 1997; Shindo et al., 1998; Fuchs et al., 1999; Scherg et al., 1999; Michel et al., 1999, 2004a; Ebersole, 2000; Ebersole and Hawes-Ebersole, 2007). However, given that simple visual analysis of an EEG recording containing focal interictal spikes usually presents no problem for an electroencephalographer to presume localization of the spike generator at a lobar or sublobar level, for ESI to be of added clinical benefit it must be able to reliably provide accurate source localizations at a much finer level.

The reliability of ESI in the clinical setting has been addressed less frequently than validity (Plummer et al., 2007, 2008). The few relevant studies have compared results obtained from modeling individual versus averaged spikes, with some evidence to suggest marked improvements in reliability with spike averaging (Bast et al., 2004, 2006). Nonetheless, most ESI continues to be performed on individual spikes or averages of a small, often unspecified, number of spikes.

The gold standard and only currently available way to accurately assess the validity of an ESI solution is through direct comparison with the intracranially recorded spike field (Merlet and Gotman, 1999; Gavaret et al., 2004; Zumsteg et al., 2005; Plummer et al., 2007, 2008). Investigations of this sort have been infrequently performed, either by comparing intracranially recorded spike fields with previous noninvasive ESI (Merlet and Gotman, 1999; Gavaret et al., 2004, 2006, 2009) or, rarely, by comparing ESI solutions with simultaneously acquired intracranial EEG spike fields (Lantz et al., 1996, 2001; Yamazaki et al., 2012).

We have recently shown that the classical anterior temporal spikes recorded in patients with MTLE are non-propagated potentials generated in the anterolateral temporal neocortex
(Wennberg et al., 2011). In this study we present a detailed analysis of multiple identical classical anterior temporal spikes recorded in a typical patient with MTLE, performed to determine the reliability and validity of ESI as applied to this most common form of interictal temporal lobe discharge. The validity of each source solution was checked against the simultaneously acquired intracranial spike field. The reliability of the ESI results was measured by comparing the solutions obtained from one spike to the next, analyzing more than 100 different examples of intracranially identical classical anterior temporal lobe spikes, recorded independently from left and right sided foci. The source solutions obtained using different combinations of forward and inverse models, different low frequency filter (LFF) settings, as well as the effects of modeling individual versus averaged spikes were all examined with the goal of assessing the potential clinical applicability of this form of noninvasive source localization.

7.2. Methods

EEG source localization was performed on data acquired during the course of presurgical clinical investigations in a patient suffering from intractable MTLE. Some data from this patient’s investigations have been presented previously (patient M5 in Wennberg et al., 2011). Brain MRI showed right hippocampal sclerosis; noninvasive scalp EEG-video monitoring demonstrated bilateral independent anterior and mid temporal spikes and ictal recordings were inconclusive as to lateralization. Combined EEG/MEG was performed, confirming the presence of bilateral right greater than left temporal lobe spikes, and, one week later, the patient underwent stereoelectroencephalographic-video monitoring for definitive localization of ictal onsets: clinical seizures were found to arise independently from both mesial temporal regions, but with a right-sided predominance at a ratio greater than 9:1. A right anteromesial temporal resection has resulted in an Engel Class IC outcome.

For the stereoelectroencephalographic recordings, intracranial EEG was acquired along with simultaneous scalp EEG (XLTEK, Oakville, ON, Canada) as described previously
(Wennberg et al., 2011). The intracranial EEG component was recorded from three bilateral 4-contact subdural strips (Ad-Tech, Racine, WI, USA) inserted through a burrhole over the second temporal gyrus of each temporal lobe, one strip running anteriorly, one posteriorly and one inferiorly, and a single 4-contact depth electrode (Ad-Tech) implanted through the same burrhole, the deepest contact aimed at the anterior hippocampus (Valiante, 2009). The burrhole was situated above the root of the zygoma, just anterior to the tragus of the ear (Valiante, 2009). Intercontact spacing for the intracranial electrodes was 1 cm. The scalp EEG component was recorded from 27 electrodes (standard 10-20 plus F9/10, T9/10, P9/10 and surface sphenoidal (zygomatic) electrodes, Sp1/2). The sampling rate was 500 Hz. Hardware (analog) filter settings with the XLTEK amplifier were 0.07 Hz (low) and 200 Hz (high).

The stereoelectroencephalographic recordings in this patient revealed six distinct, independent neocortical temporal lobe spike foci: right anterolateral, right mesiobasal, left anterolateral, left anterobasolateral with anterior to posterior neocortical propagation, left lateral, and left mesiobasal (described previously in Wennberg et al., 2011). In this study we analyze in detail the right anterolateral spike focus because (a) it represents an archetypal example of the classical anterior temporal lobe EEG spike pattern seen in MTLE, and (b) abundant spikes from this same right anterior temporal lobe focus were recorded during the EEG/MEG investigation, allowing for direct comparison of EEG and MEG source localization results. A detailed examination of the MEG source imaging (MSI) solutions obtained for these right anterior temporal lobe spikes is the subject of a separate paper (Wennberg and Cheyne, 2014a).

Fig. 7.1 shows the intracranial and scalp EEG fields of the right anterior temporal lobe spike focus. The spike generator was localized entirely to the anterolateral temporal neocortex, with no evidence of propagation elsewhere in the temporal lobe.

The contralateral left anterolateral EEG spike focus was also analyzed to ensure reproducibility of the ESI results.
7.2.1. EEG spike selection

A continuous 4-hour segment of stereoencephalographic recording was analyzed for interictal spikes, which were manually reviewed and selected using Insight software (Persyst, Prescott, AZ, USA) as described previously (Wennberg et al., 2011). Sixty-four right anterior temporal lobe spikes with the same intracranial morphology and field of distribution were arbitrarily selected from a total of 142 similar spikes for subsequent averaging and analysis. Fig. 7.2 shows 16 of the spikes (numbers 17-32), demonstrating an essentially identical intracranial field for each individual spike (Fig. 7.2A), and showing also each spike’s associated scalp EEG waveform (Fig. 7.2B). Spikes 1-16 and 33-64 are similarly depicted in Supplementary Figs. 7.S1-7.S3. Visual analysis of the intracranial spike fields clearly reveals that the spikes arise from within the same focus. The surface negative anterolateral temporal neocortical spike peak that appears with maximal amplitude at subdural contact RTA2 shows a consistent amplitude decrement of more than 50% at the subdural contacts situated 1 cm anteromedially and 1 cm posterolaterally to RTA2, with the spike potential essentially isoelectric at the subdural contact situated 2 cm posterolaterally to the peak maximum at RTA2 (Fig. 7.2, Supplementary Figs. 7.S1-7.S3). The depth electrode contacts situated in the subcortical temporal white matter posterior to the cortical spike source show a synchronous, low amplitude waveform, inverted in polarity, representing the volume conducted electropositive field of the “opposite” side of the anterior temporal cortical dipole layer, as is typical for classical anterior temporal lobe spike generators in patients with MTLE (Wennberg, 2010a; Wennberg et al., 2011). Quantitatively, the mean maximal peak to peak amplitudes for the 64 right anterior temporal spikes, measured at the different intracranial electrode contacts, were: RTA1 = 982 (± 228) µV; RTA2 = 2,831 (± 563) µV; RTA3 = 1,310 (± 425) µV; RTA4 = 419 (± 238) µV; RTD4 = 565 (± 212) µV (the waveform inverted in polarity at the latter site). Mean peak to peak amplitudes were below 260 µV at all other intracranial electrode contacts. The corresponding mean spike amplitude ratios at the different intracranial electrode contacts (as a percentage of the maximum peak to peak amplitude
at RTA2) were: RTA1 = 35% (± 7%); RTA3 = 45% (± 10%); RTA4 = 14% (± 8%); RTD4 = 20% (± 7%). Spike amplitude ratios were ≤ 9% at all other intracranial electrode contacts.

A total of 48 independent contralateral left anterior temporal lobe spikes with a homologous morphology and distribution were recorded during the same 4-hour segment and these were also selected for comparative analysis.

7.2.2. Source localization

Source localization of individual and averaged spikes was performed using CURRY 6 (Abbotsford, Victoria, Australia). Spike epochs were generated using a time window from -750 to +250 ms relative to the negative peak (which invariably occurred simultaneously in the intracranial EEG and scalp EEG recordings). The interval selected for source localization analyses of single and averaged right anterior temporal spikes was from -50 to +6 ms, representing the time from spike onset to just after peak (t = 0 ms) latency (for the left anterior temporal spikes the interval was -30 to +14 ms, peak at t = 4 ms). Given the intracranial EEG evidence that the spikes were neither propagated from nor to other regions in the temporal lobe (Figs. 7.1 and 7.2), modeling was performed on the spike peaks. For comparative purposes, modeling was also performed at the mid upswing of the right anterior temporal spikes. Noise level was estimated as the variance of the data in the signal from -750 to -250 ms before each individual or averaged spike. Electrode positions were registered through label-matching within CURRY 6. A common average reference of all scalp electrodes was used for source localization. The software high frequency filter (HFF) setting was 30 Hz. Three different LFF software settings were tested: 1 Hz, 3 Hz and 6 Hz.

To assess the physiologic validity of dipole source localizations, solutions were compared against the known intracranial cortical generator. The localization of the subdural electrode contact marking the site of maximal right anterior temporal spike amplitude was plotted on the patient’s high resolution brain MRI (through co-registration of the pre-operative MRI and the
MRI obtained after implantation of intracranial EEG electrodes; Fig. 7.3A,B). Next, an area bounding the cortical surface extent of the intracranially-defined spike field was drawn on the MRI extending outward from the point of maximum spike amplitude to delimit the extent of the cortical field (as indicated by the intracranial EEG recording). Finally, the cortical boundary was closed approximately 1 cm deep to the cortical surface into an ellipsoid pattern, superimposed on the patient’s high resolution brain MRI in CURRY 6 (Fig. 7.3C). The choice of 1 cm was arbitrary, based on a clinical judgment of what would represent an acceptable level of source localization accuracy, better than achieved by visual examination, but close enough to the cortical surface to infer a superficial cortical localization. It was felt that a smaller depth, e.g., 0.5 cm, would be placing unreasonable expectations upon current noninvasive source localization techniques. On the other hand, a deeper boundary, e.g., 1.5 or 2 cm, would create an area so large as to no longer be justifiable as a level of localization that could be fairly conceived as adding value to a routine clinical EEG investigation (i.e., localization to a sublobar area this large could likely be determined simply by looking at the topographic distributions of spikes in the raw data).

For the purposes of this study, dipole source solutions in CURRY 6 that were localized within the defined generator boundary were deemed to be correctly localized. Dipole orientations were deemed correct if dipole vectors projected outward through the anterolateral temporal neocortex between the anterior and posterior extent of the cortically outlined spike field boundary. (A similar process was performed to outline the approximate extent of the cortical generator field on the Montreal Neurological Institute (MNI) averaged brain MRI.)

The comparative effects of different forward models, LFF settings and spike averaging on the validity of source localization results were analyzed quantitatively using the non-parametric Mann-Whitney U test, with each spike (or averaged spike) given a ranking of 0, 1, 2 or 3, where 0 = localization and orientation both incorrect, 1 = localization incorrect, orientation correct, 2 = localization correct, orientation incorrect, 3 = localization and orientation both correct. Correct localization alone was ranked higher than correct orientation alone given the
greater clinical utility of accurate localization. The statistical analyses were not performed on averages of 16 or more spikes (i.e., where total n < 5).

7.2.3. Forward models

The effects on EEG source localization of different forward models (volume conductors; Fuchs et al., 2001, 2007) were assessed by comparing results obtained using two different realistic volume conductors: (a) an individualized model created from the patient's own MRI using the boundary element method (BEM), or (b) a non-individualized model created from the MNI averaged MRI dataset using the finite element interpolated method (FEM). The latter model is geometrically less accurate (and numerically more accurate) than the individualized BEM volume conductor. The results obtained using the FEM model were assessed only because of the potential clinical ease of use of a non-individualized volume conductor, which does not require MRI data acquisition and a separate forward model calculation for each patient (Plummer et al., 2007, 2010a,b). Both models were created within the CURRY 6 software platform.

7.2.4. Inverse models

Dipole mapping was performed using the fixed coherent dipole modeling algorithm in CURRY 6, corresponding to the classical equivalent current dipole model.

For selected individual spikes, the effects of regularization on the dipole modeling algorithm were assessed, using a weighting (regularization parameter) of $\lambda = 1.0$ (eliminating dipole components with a contribution to the forward-fit signal < 1.0 of the signal to noise ratio (SNR) at a given time point; Michel et al., 2004a; Plummer et al., 2007, 2010a,b). Confidence ellipsoids (CEs) shown surrounding dipole solutions indicate regions within which changes in forward calculated data would be below noise compared to the forward calculated data obtained for the best-fit dipole location (Fuchs et al., 2004).
Distributed source modeling was performed using sLORETA (Pascual-Marqui, 2002; Wagner et al., 2004). The effects of different solution subspace choices on localization were examined by comparing the results obtained using (a) a cortically constrained subspace with rotating sources and (b) a cortically constrained subspace with fixed normal sources, either unextended or extended over a 20 mm patch (Plummer et al., 2010a,b). The effect of thresholding on distributed source solutions was examined by comparing cutoff thresholds of 50% and 75% (where solutions with smaller explained field percentages (as a percentage of the largest current) are excluded from display).

7.2.5. Data preprocessing

For selected individual spikes, the effects on source localization of preprocessing the EEG data using principal component analysis (PCA) and independent component analysis (ICA) were analyzed in CURRY 6. In this de-noising procedure, PCA was first performed on the data to identify orthogonal (uncorrelated) components, which then underwent ICA to identify statistically independent signal components. Mean global field orthogonal signal components of spikes with a SNR > 1.0 identified by PCA underwent ICA (Onton et al., 2006; Plummer et al., 2007, 2010a,b).

7.2.6. Spike averaging

To assess the effects on source localization of spike averaging, solutions obtained from modeling individual spikes were compared to solutions obtained from modeling averages of 2, 4, 8, 16, 32 and the grand average of 64 spikes for the right temporal focus (48 for the left temporal focus). Spikes were averaged in progressively larger groups moving from left to right on the number line (e.g., averages of 2 spikes comprised spikes 1-2, 3-4, ... 63-64, averages of 4 spikes comprised spikes 1-4, 5-8, ... 61-64, and so on).
7.3. Results

7.3.1. ESI of right anterior temporal lobe spikes

Fig. 7.4 shows the dipole source solutions obtained for the grand average of the 64 right anterior temporal spikes with a LFF setting of 1 Hz, using both the non-individualized FEM as well as the individualized BEM forward models. Physiologically valid solutions were obtained using both volume conductors, with localization co-ordinates within 0.14-0.76 cm of the intracranially-identified cortical source maximum in all three planes. The largest displacement from the true intracranial source maximum was seen as an inferior shift in the $z$ plane with the non-individualized FEM head model.

Fig. 7.5 shows the distributed source modeling solution obtained through application of sLORETA to the same EEG data, using a cortical subspace constraint with fixed normal sources in a 20 mm extended patch. The focal maximum within the distributed solution was localized near to the intracranially-identified anterior temporal cortical source maximum (within 0.33-1.05 cm in $x$, $y$, $z$ planes). The distributed solution underestimated somewhat the extent of the true cortical field, especially if the cutoff threshold for display was increased to remove more distant “ghost sources” (Fig. 7.5B). sLORETA using different solution subspaces (rotating sources or fixed sources with no extension) also returned right anterior temporal solutions, but their maxima were slightly further away from the true intracranial source (not shown).

Supplementary Fig. 7.S4 shows the dipole source solutions for the 64 individual right anterior temporal spikes analyzed using the FEM volume conductor. Despite the near-identical intracranial field of each spike, source solutions were scattered around the right temporal region, including occasional dipole sources situated outside the right temporal lobe, as far away as the contralateral hemisphere. With the 1 Hz LFF only 11 of the 64 dipole sources were physiologically valid. Compared to the 1 Hz LFF, the reliability of dipole source solutions was improved and the proportion of valid solutions increased with the 3 Hz LFF ($25/64, p = 0.017$; Supplementary Fig. 7.S4B) and the 6 Hz LFF ($22/64, p = 0.020$; not shown). Nonetheless, more
than half of all individual spike dipole source solutions obtained with the FEM forward model were physiologically invalid, even with the higher LFF settings. Further results obtained in analyses using the FEM volume conductor are presented in Supplementary material.

Fig. 7.6 shows the dipole source solutions for the same 64 individual right anterior temporal spikes analyzed using the BEM volume conductor. Source solutions obtained with the BEM forward model were more reliable and the proportion of physiologically valid solutions increased compared with those obtained with the FEM forward model (22/64 vs. 11/64, \( p = 0.017 \) for LFF = 1 Hz; 36/64 vs. 25/64, \( p = 0.019 \) for LFF = 3 Hz; 41/64 vs. 22/64, \( p = 0.009 \) for LFF = 6 Hz). However, even with the BEM forward model, some spikes were associated with markedly incorrect dipole source localizations or orientations. Source solutions were more reliable and more likely to be physiologically valid with the 3 Hz LFF (\( p = 0.008 \); Fig. 7.6B) and the 6 Hz LFF (\( p = 0.010 \); not shown) than with the 1 Hz LFF. Nonetheless, more than a third of all individual spike dipole source solutions obtained with the BEM forward model were physiologically invalid, even with the higher LFF settings.

Data preprocessing of individual spikes with PCA/ICA and/or regularization did not reliably improve the localization or orientation of mislocalized dipole sources, and occasionally valid source solutions obtained without data preprocessing were rendered invalid with preprocessing (Supplementary Fig. 7.S5).

In general, distributed source modeling of individual spikes with sLORETA did not improve upon the localization validity obtained with dipole mapping, nor did it provide useful information regarding the extent of the true cortical spike field (see Supplementary material, Supplementary Fig. 7.S6).

7.3.2. Goodness-of-fit and SNR

For individual spikes, dipole source goodness-of-fit (expressed as % explained variance, \( V \)) and SNR were positively correlated (linear regression: \( R^2 = 0.154; p < 0.001 \), for BEM
forward model, 1 Hz LFF). Mean values of $V$ and SNR for individual spike dipole sources were significantly greater with LFF settings of 3 Hz and 6 Hz ($t$-test: both $p < 0.01$) than with a LFF setting of 1 Hz (Table 7.1, top row). However, the goodness-of-fit of an individual dipole source solution was not a reliable predictor of valid dipole source localization and orientation for individual spikes, even with the higher LFF settings. Using the best combination of BEM forward model and 3 Hz LFF, the proportion of correctly localized and oriented individual spike dipole sources was higher among dipole solutions with $V > 90\%$ (23/35) than among dipole solutions with $V < 90\%$ (13/29), however, this difference was not significant ($p = 0.13$) and approximately one third of dipole source solutions with $V > 90\%$ were not physiologically valid (Fig. 7.7). Requirement for an even higher goodness-of-fit, e.g., $V > 95\%$, excluded most dipole source solutions. With LFF = 1 Hz, only 2/64 dipole sources met a criterion of $V > 95\%$ (both invalid solutions); with LFF = 3 Hz, 8/64 dipole sources had $V > 95\%$ (3 of the 8 solutions were valid; Fig. 7.7).

Similarly, SNR was not a reliable predictor of valid dipole source localization for individual spikes, although the worst mislocalizations (e.g., incorrect hemisphere or posterior to the sagittal midpoint) tended to have lower SNRs (e.g., below 2). Supplementary Fig. 7.S7 demonstrates representative relations between SNRs and dipole source localizations in the $x$ and $y$ planes for individual right anterior temporal spikes.

7.3.3. Modeling at mid upswing of spike

Modeling performed at the mid upswing of the grand averaged spike returned a valid source solution using the BEM volume conductor (within 0.03-0.49 cm of the true intracranial source maximum in all three planes), with a smaller dipole moment and slightly larger CE than that obtained with modeling at the peak (Fig. 7.8A).

The reliability and validity of dipole source solutions obtained from modeling single spikes at the spike mid upswing was poor (Fig. 7.8B). Mean SNR for individual spikes was lower
(1.42 ± 0.5) and mean $V$ much lower (57.6 ± 27.5) than the corresponding values for single spikes modeled at the peak (Table 7.1).

7.3.4. Spike averaging

Averaging of spikes was associated with significant improvements in the validity of source localization results. Averaging of 2 or more spikes improved SNR, $V$, reliability of source solutions and the proportion of valid solutions at all three tested LFF settings (see Table 7.1 and Supplementary Fig. 7.S8). CEs surrounding source solutions progressively decreased in size with increasing number of spikes averaged, and were consistently smaller with the BEM, as opposed to FEM, forward model after averaging 2 or more spikes (see Supplementary Table 7.S1).

Comparing the effects of the 3 Hz and 6 Hz LFF settings on the results obtained for averaged spikes showed both to be associated with increased mean SNR and $V$ values as compared to the 1 Hz LFF setting, most evident with the 3 Hz LFF (Table 7.1). Mean amplitudes of dipole sources were similar with the 1 Hz and 3 Hz LFF settings, but were consistently lower with the 6 Hz LFF (Table 7.1). The dipole source localization obtained for the grand average of all 64 spikes was essentially identical for the 1 Hz and 3 Hz LFF settings, and slightly further away from the true intracranial source with the 6 Hz LFF (Supplementary Fig. 7.S8).

7.3.5. Averaged versus individual spikes; LFF effects; BEM volume conductor

Using the BEM volume conductor, the proportion of valid dipole source solutions was significantly increased after averaging 4 or 8 spikes with LFF = 1 Hz ($p < 0.005$ and $p < 0.05$, respectively) and after averaging 4 spikes with LFF = 3 Hz ($p < 0.01$) as compared with the analyses performed on single spikes.

Comparing the effects of the three LFF settings on averaged spikes revealed no significant differences in the numbers of valid source solutions obtained after averaging 2, 4 or 8 spikes.
Fig. 7.9 shows the source localization and orientation results obtained for individual spikes and the different averaged spike combinations using the BEM volume conductor and the LFF = 1 Hz and LFF = 3 Hz settings.

Fig. 7.10 shows the dipole source solutions for the averages of 8 spikes using the BEM volume conductor and the LFF = 1 Hz and LFF = 3 Hz settings, and the associated goodness-of-fit levels, the latter not contributory to more or less valid dipole source solutions for the averaged spikes.

7.3.6. ESI of left anterior temporal lobe spikes

Source localization results similar to those described for the right anterior temporal lobe spikes – with respect to the effects of low frequency filtering and spike averaging upon the reliability and validity of dipole source solutions – were found with the analyses performed on the 48 contralateral left anterior temporal spikes, and these results are depicted in Fig. 7.11, Supplementary Fig. 7.S9 and Supplementary Fig. 7.S10.

7.4. Discussion

Noninvasive source localization, or source imaging, holds promise for determining the particular region(s) of the brain responsible for generating the waveforms recorded outside the skull with EEG or MEG. The idea that one may accurately solve this “inverse problem” of neurophysiology, formulated by Helmholtz more than 150 years ago (Helmholtz, 1853), may at first appear fanciful as the inverse problem does not have a unique solution. In other words, the problem is considered by definition to be ill-posed. Nevertheless, empirical evidence accumulated over recent decades has enabled many advances in source imaging techniques, and the ability to constrain inverse solutions to only those that are physiologically plausible has increased the face validity of results. In the field of epilepsy, where accurate determination of the brain region(s) responsible for generation of epileptiform activity is vital for the surgical treatment of patients, it
has been proposed that noninvasive source imaging using EEG, or ESI, has now advanced to the point that it may be ready to play a role in routine clinical investigation (Plummer et al., 2007, 2008; Brodbeck et al., 2011).

The purpose of this study was to perform a detailed reliability analysis of the source solution results obtained when performing ESI on a large collection of identical spikes. The validity of the source solutions was assessed by direct comparison with the simultaneously acquired intracranial recordings. The results showed that ESI performed on averaged spikes from a classical anterior temporal lobe spike focus was able to depict the true intracranial cortical source maximum with surprisingly high (subcentimeter) accuracy, using only a standard clinical array of 27 EEG electrodes. For this archetypal anterolateral temporal neocortical spike source, which is known to have a cortical extent of approximately 10-20 cm$^2$ (Tao et al., 2007), ESI of averaged spikes did not provide solutions falsely localized deep to the true superficial cortical source, which is in contrast to ESI results obtained for larger, bilateral sources, such as the human K-complex, where deep mislocalizations appear to be inevitable output solutions of both dipole mapping and distributed source modeling algorithms (Wennberg and Cheyne, 2013). The upper size limit of an extended cortical source that may be accurately modeled with existing noninvasive source imaging techniques is unknown, but must lie somewhere between the 10-20 cm$^2$ of an anterior temporal spike focus and the much larger bifrontal cortical distribution of the K-complex.

7.4.1. Reliability and validity of ESI performed on single spikes

The validity of source localization solutions obtained in the analysis of single spikes was inconsistent, i.e., modeling performed on individual anterior temporal spikes was not highly reliable. Reliability (and the proportion of valid solutions) was better with a LFF setting of 3 Hz (and, to a lesser extent, 6 Hz) as compared to a 1 Hz LFF setting, likely reflecting the greater
mean SNR obtained with the higher LFF settings (despite the observation that for any given single spike, a high SNR was not a strong predictor of a valid source solution).

Data preprocessing using PCA and ICA, and the application of regularization to the dipole mapping algorithm, techniques that have been proposed to potentially increase the validity and reliability of ESI (Michel et al., 2004a; Plummer et al., 2007, 2010a,b), had no beneficial effect in this study, and in fact source solutions were occasionally rendered less valid after application of these methods.

High goodness-of-fit values (e.g., $V > 90\%$) for individual spike dipole sources were associated with a greater likelihood of valid source solutions, although the association was not statistically significant. Similar to SNR, for any given single spike, a high $V$ was not a reliable predictor of a valid source solution. Even using the best combination of BEM forward model and 3 Hz LFF approximately one third of dipole source solutions with $V > 90\%$ were not physiologically valid, suggesting that ESI of single spikes may not be sufficiently reliable for clinical investigation.

7.4.2. Dipole source scatter of individual spikes represents the limited reliability of ESI and not the extent of epileptogenic cortex

In this study, the true cortical source of each spike was known to be identical from the simultaneous intracranial EEG recordings such that any scatter of ESI solutions could be directly attributed to limitations in reliability of the noninvasive source localization methodology. From the results reported here, it would appear that clusters of scattered dipole sources should not be taken as evidence of the extent of the brain region responsible for generation of the extracranially-recorded spikes. Instead, at least as a first hypothesis, scattered clusters of dipole sources should be taken as a sign suggesting limited reliability of the source imaging method. The evidence presented in this study is limited to typical, non-propagated anterior temporal lobe spikes, however, there is no reason to expect that the implications of dipole source scatter might
not apply equally to focal spike generators situated in other brain regions. In fact, strong evidence supporting the idea that scattered dipole sources represent limitations in the reliability of ESI performed on single spikes, rather than the extent of an epileptogenic brain region, has been previously published (Bast et al., 2004, 2006).

7.4.3. Reliability and validity improved with spike averaging

Spike averaging was the single most effective operator dependent intervention in the source imaging methodology and it was able to improve both the reliability and validity of ESI. Despite the fact that the data were acquired using just 27 scalp EEG electrodes during the patient's routine clinical investigations, ESI performed on averaged topographically identical focal spikes was associated with subcentimeter level localization accuracy as determined by direct comparison with the simultaneously acquired intracranial EEG spike field.

SNR, goodness-of-fit, reliability of source solutions and the proportion of valid source solutions progressively increased with averages of greater numbers of spikes, at all three of the LFF settings tested and with both of the tested volume conductors. Statistically significant improvements in the proportion of valid source solutions were noted with averages of 4 spikes, the significance further improving with averages of 8 or more spikes. Indeed, the benefits identified with the higher LFF settings in ESI performed on single spikes (presumably attributable to selective reduction of low frequency background activity components, which are typically of larger amplitude than higher frequency background activity and thus likely to contribute relatively more power to the background noise) became insignificant once 4 or more spikes were averaged. Interestingly, the known benefits of an individualized realistic volume conductor (confirmed in this study in the analysis of single spikes) essentially disappeared when averages of 8 or more identical spikes were used for ESI.

Although the role of spike averaging prior to ESI in the clinical investigation of epilepsy is considered to be an unresolved issue (Plummer et al., 2007, 2010a,b), the findings in this study
align well with the few previous reports that have systematically addressed the issue of spike averaging (Krings et al., 1999; Bast et al., 2006). In this study, the numbers of averaged spikes were selected arbitrarily as exponents of the number 2 and no clear cutoff can be suggested as the lower limit of spikes to average to optimize ESI reliability and validity. Significant benefits were seen with averaging as few as 4 spikes, however, benefits clearly further improved when averaging 8 spikes and appeared to improve even more when averaging larger numbers of identical spikes, the benefits continuing to improve in terms of increased SNR and $V$, and decreased CE volume, all the way up to the averages performed on 32 and even 64 spikes. From the results presented, a lower limit for spike averaging might be suggested to be somewhere around 8 spikes. Interestingly, Krings et al. (1999) in a simulation study determined that between 10 to 20 averaged sine wave pulses were needed to achieve localization results accurate to within 2.5 cm (10 pulses when 41 EEG electrodes were used and 20 pulses when 21 EEG electrodes were used) and these authors suggested that “as a rule of thumb” at least 10 spikes should be averaged to obtain reliable dipole source localization and that ideally more than 30 spikes should be averaged (Krings et al., 1999). In a clinical study, Bast et al. (2006) determined that to reduce dipole source scatter below 2 cm in 95% of cases one needed to average at least 10 spikes (when modeling at the spike peak) or 25 spikes (when modeling at mid upswing; Bast et al., 2006).

The benefits of spike averaging are clear and presumably result primarily from increasing the SNR of the modeled spike through the progressive diminution of background EEG activity that is realized with increasing numbers of averaged spikes, rendering the signal more and more analogous to an evoked potential.

A crucial requirement in the averaging process as applied to epilepsy, unlike evoked potential recordings, is that one must ensure that only “identical” spontaneous epileptiform potentials are grouped for averaging. Currently, such a process cannot be automated without compromising the accuracy of determination of identicality of the spike field. At this point, careful analysis of the topographic distribution of individual spontaneous spikes by a trained
electroencephalographer is necessary to ensure that only spikes arising from a single focus are included in the averaging process. For example, in patients with MTLE, multiple spike foci are common within one or both of a patient's temporal lobes (as in the patient examined in this study; Wennberg et al., 2011). Mixing T4 maximum, horizontally oriented, mid temporal spikes with F8 maximum, obliquely oriented, anterior temporal spikes would nullify the benefit of spike averaging. In clinical practice, however, different spike foci are usually separable by a qualified electroencephalographer through a careful analysis of the associated voltage topographic fields, even if the foci are situated within the same lobe of the brain. Nonetheless, it must be acknowledged that this stage of the process requires a time commitment and necessary attention to detail that cannot be ignored in considerations of the potential impact of incorporating ESI in the routine clinical management of patients with epilepsy.

Another issue of clinical relevance related to spike averaging is the need to capture a sufficient number of identical spikes. This could prove to be difficult to accomplish in many patients in the outpatient laboratory setting. However, all patients undergoing presurgical investigations will presumably undergo at some point continuous high quality EEG-video recording and for most patients this already routine stage of investigation should be sufficient to capture enough spikes to enable spike averaging for source imaging purposes.

7.4.4. Dipole mapping versus distributed source modeling

The accuracy of localization of source maxima was similar between the two inverse models tested, the fixed coherent dipole mapping method and sLORETA, the latter a minimum norm estimation based distributed source modeling algorithm. In general, distributed source modeling of individual spikes with sLORETA did not improve upon the localization of source maxima obtained with dipole mapping.

In that the true cortical source of a spontaneous interictal epileptiform discharge is distributed over an extent of cortex, it is conceptually appealing to think that a distributed source
Localization algorithm might be able to provide an estimation of the extent of the cortical spike generator. However, for the anterior temporal lobe spike field examined in this study, sLORETA was unable to provide useful information pertaining to the cortical extent of the spike generator. Moreover, the use of arbitrarily selected cutoff thresholds introduces a non-evidence-based operator bias to the displayed sLORETA results, decreasing objectivity and limiting potential clinical utility for determination of the extent of epileptogenic cortex. In this study, for example, thresholding performed on the grand averaged spike to remove “ghost” sources resulted in an sLORETA solution that underestimated the extent of involved cortex, whereas the same threshold applied to individual spikes was associated with large overestimations of the extent of the cortical source.

7.4.5. Spike peak versus mid upswing modeling

Whether ESI should be performed at the spike peak or mid upswing is a matter of debate (Merlet and Gotman, 1999; Ebersole, 2000; Lantz et al., 2003b; Bast et al., 2006; Ray et al., 2007; Ebersole and Hawes-Ebersole, 2007; Plummer et al., 2010b, Wang et al., 2011). In this study, modeling performed at the mid upswing of the grand averaged spike, although associated with a lower SNR, lower goodness-of-fit and larger CE than that obtained with modeling at the spike peak, provided a physiologically valid source localization (with the BEM volume conductor) that differed little from that obtained with modeling the grand average at the spike peak. However, in the analysis of single spikes, mean SNR and mean \( V \) were markedly reduced when modeling was performed at the mid upswing, and the source solutions obtained were less reliable and less likely to be accurately localized. A more complete discussion of these findings can be found in the Supplementary material.

7.4.6. Number of EEG electrodes
Many studies have demonstrated improved source localization parameters with higher numbers of scalp EEG electrodes, almost certainly attributable to the improved spatial resolution obtainable with higher density EEG recording (Lantz et al., 2003a; Meckes-Ferber et al., 2004; Plummer et al., 2007; Brodbeck et al., 2011; Wang et al., 2011; Yamazaki et al., 2012). Although the optimal number of EEG electrodes is unknown, evidence suggests that the most important additional electrodes beyond the standard 19 electrode 10-20 array are those situated along the subtemporal line (Ebersole and Wade, 1991; Meckes-Ferber et al., 2004; Plummer et al., 2007), electrodes that were included in the recordings analyzed in this study and which are easily added for routine clinical investigations during continuous EEG-video monitoring.

Higher density EEG recording would likely have increased the reliability and validity of ESI performed on individual spikes in the current study. Nonetheless, in consideration of a practical clinical role for ESI in the presurgical investigation of epilepsy, high density EEG recording would require an additional examination, one which in many patients would be insufficient in duration to capture enough spikes to permit appropriate spike averaging.

7.4.7. Effects of skull foramina

The presence of a skull burrhole at the site of intracranial electrode implantation must be acknowledged as a potential limitation in this study, in that a breach effect related to the burrhole could theoretically alter the normal pathways of electrical conductivity from the temporal cortex to the scalp. However, in this particular case, the single burrhole was situated quite posterior to the intracranial spike source, and there was no visibly evident breach effect at any of the scalp electrodes. In a study examining simultaneously recorded intracranial and extracranial temporal lobe spike voltage fields, Tao et al. (2007) found that alterations in scalp EEG fields due to burrholes or even craniotomies for intracranial electrode placement were uncommon in the absence of very large skull defects.
The question of the effects of skull foramina on the extracranially recorded fields of anterior temporal spikes is not limited to burrholes and craniotomies, but also includes consideration of the holes in the skull around the orbit, specifically the superior orbital fissure, the optic foramen and the foramen ovale. A series of studies from the King’s College group in London has presented evidence acquired from: (a) EEG compared with subsequent acute electrocorticographic recordings (Fernández Torre et al., 1999a), (b) simultaneous EEG and foramen ovale recordings (Fernández Torre et al., 1999b; Nayak et al., 2004), and (c) EEG using additional periorbital and cheek electrodes (Sparkes et al., 2009) to suggest that different intracranial temporal lobe spike generators may all produce anterior temporal scalp EEG spike maxima because of preferential conductivity of the electrical fields through the anterior skull foramina.

The spikes analyzed in this study were all known from intracranial recordings to be generated within the superficial anterolateral temporal neocortex, and so the results presented do not specifically address the question of whether more posteriorly localized cortical spikes (as determined from simultaneous intracranial recordings) might similarly be associated with anterior temporal scalp maxima. In a preliminary analysis relevant to this question, we have analyzed the 18 spikes recorded from this patient’s left lateral (mid) temporal neocortical focus (described previously in Wennberg et al., 2011), and found source solutions to be localized more posteriorly than sources associated with spikes arising from the left and right anterolateral temporal neocortical foci, in keeping with the different scalp EEG topographies (Supplementary Fig. S11). However, only 18 spikes were available for analysis from this lateral temporal focus, and their intracranial source was situated much closer to the overlying skull burrhole used for implantation of the intracranial electrodes, such that any interpretation of these results with respect to the general effects of skull foramina on temporal lobe spike fields must be considered with circumspection.
7.4.8. Recommendations

Recommendations based on this single study may not be generalizable to spike foci situated in other brain regions. Nonetheless, the anterolateral temporal neocortical spike generators investigated here represent the most common of all spike foci in adults with epilepsy and it is reasonable to assume that many of the observations regarding reliability and validity of ESI in this particular setting may also apply to foci situated in other brain regions. It is likely, however, that recommendations derived from observations in this study may not be applicable to widespread, bilaterally synchronous epileptiform discharges or to generalized spike and wave complexes, as such widespread synchronized cortical sources are unlikely to be amenable to noninvasive source localization, and highly likely to be subject to the severe limitations on ESI accuracy demonstrated in attempts to model the human K-complex (Wennberg and Cheyne, 2013). Whether or not large unilateral extratemporal spike foci present problems similar to those associated with the bilaterally synchronous fields or may instead prove to be amenable to existing source localization techniques is an important question for future research in noninvasive source imaging.

The main recommendation to be derived from the results of this study is that ESI of single spikes should be avoided as a clinical tool. Spike averaging, ideally of at least 8 carefully selected topographically identical spikes – preferably more – should be performed prior to ESI whenever possible.

If individual spikes must be analyzed, the reliability and validity of source localization is improved through use of a LFF setting of at least 3 Hz. A 6 Hz LFF did not significantly improve upon the benefits seen with the 3 Hz LFF and in some situations was associated with more spurious results. LFF settings between 3 and 6 Hz were not tested in this study.

An important result of this study was the demonstration that dipole source scatter is a reflection of the imperfect reliability of the source imaging methodology and not an estimation of the extent of cortical epileptogenicity. The identification of individual spike dipole source clusters
might provide rough guidance to differentiate localization of a spike generator at the lobar level, e.g., frontal lobe versus temporal lobe. However, the observed dipole source cluster is related to fallibilities of the source localization technique when modeling single spikes – precise intralobar localization of the true focal spike source maximum cannot be derived from a cluster of scattered dipole sources. The ability to perform ESI on averages of carefully selected topographically identical spikes appears to be of paramount importance with respect to obtaining precise intralobar localization of the sort that could provide real added value to clinical presurgical investigation.

Given the clear benefits in terms of SNR associated with modeling performed at the spike peak, it is recommended that ESI should be routinely performed at the spike peak, rather than at the mid upswing (discussed further in Supplementary material).

Finally, the demonstration of extremely good spike localization accuracy attainable using only a standard clinical EEG electrode array, combined with the observation that recording a sufficient number of identical spikes for spike averaging may be the most important modifiable factor, suggests that the most expedient and cost-effective way to integrate noninvasive source imaging into the routine clinical presurgical management of epilepsy patients may be to incorporate ESI into the analysis of the data currently acquired during continuous EEG-video monitoring.
Table 7.1. SNR and $V$ of right anterior temporal EEG spikes; individual (n=64) and averaged (2$, x=1,2,3...6$) spikes, different LFFs (1 Hz, 3 Hz, 6 Hz).

<table>
<thead>
<tr>
<th>EEG</th>
<th>LFF 1 Hz</th>
<th>LFF 3 Hz</th>
<th>LFF 6 Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amp. (µAmm)</td>
<td>SNR (%)</td>
<td>Amp. (µAmm)</td>
</tr>
<tr>
<td>Ind. Spikes (n=64)</td>
<td>746.8 ± 671</td>
<td>2.00 ± 0.7</td>
<td>87.0 ± 5.9</td>
</tr>
<tr>
<td>Av. 2 spikes (n=32)</td>
<td>556.4 ± 334</td>
<td>2.69 ± 0.8</td>
<td>89.6 ± 5.7</td>
</tr>
<tr>
<td>Av. 4 spikes (n=16)</td>
<td>559.5 ± 214</td>
<td>3.85 ± 1.0</td>
<td>91.3 ± 4.5</td>
</tr>
<tr>
<td>Av. 8 spikes (n=8)</td>
<td>526.0 ± 249</td>
<td>4.76 ± 1.1</td>
<td>92.6 ± 3.5</td>
</tr>
<tr>
<td>Av. 16 spikes (n=4)</td>
<td>599.9 ± 216</td>
<td>7.15 ± 0.9</td>
<td>93.1 ± 3.1</td>
</tr>
<tr>
<td>Av. 32 spikes (n=2)</td>
<td>544.7 ± 15</td>
<td>9.2 ± 2.5</td>
<td>94.2 ± 0.8</td>
</tr>
<tr>
<td>Av. 64 spikes (n=1)</td>
<td>580.5 ± 13.3</td>
<td>95.2</td>
<td>578.1 ± 15.3</td>
</tr>
</tbody>
</table>

Amp.=amplitude, Av.=average, Ind.=individual, LFF=low frequency filter, SNR=signal to noise ratio, $V$=variance

**$p<0.01$ (compared with LFF 1 Hz value); *=p<0.05 (compared with LFF 1 Hz value)
Fig. 7.1. Averaged right anterior temporal lobe spike waveform in patient with mesial temporal lobe epilepsy and right hippocampal sclerosis. Stereoelectroencephalographic recordings obtained during presurgical clinical investigations. Spikes averaged on intracranial contact with maximal peak amplitude (RTA2; n = 64). The neocortical spike localization is associated with an anterior temporal scalp EEG spike field maximal at F8, F10, Sp2 (right zygomatic (surface sphenoidal electrode). Sensitivity 70 μV/mm for intracranial EEG, 10 μV/mm for scalp EEG; common average reference montage for both scalp and intracranial EEG, the average reference comprising 12 scalp electrodes (F3, F4, C3, C4, P3, P4, O1, O2, T3, T4, T5, T6); LFF 0.5 Hz, HFF 70 Hz.
Figure 7.2A
Fig. 7.2B. Stereoelectroencephalographic recordings of individual right anterior temporal spikes 17,18,19...32 (from the 64 spikes averaged in Fig. 7.1). (A) Intracranial EEG. (B) Simultaneous scalp EEG. Common average reference and filters as in Fig. 7.1.
Fig. 7.3. (A) Subdural electrode contact (RTA2, green crosshairs) marking neocortical site of maximal right anterior temporal spike amplitude. (B) Localization of right anterior temporal spike maximum on patient’s pre-operative high resolution MRI (green crosshairs; $x = 47.5$ mm, $y = 34.6$ mm, $z = 18.9$ mm). Localization obtained through co-registration of pre-operative MRI with MRI obtained after implantation of intracranial EEG electrodes. (C) Area within which dipole source localizations were deemed physiologically valid (green outline). Orientations were deemed valid if dipole vectors projected out through the right anterolateral temporal neocortex somewhere between the anterior and posterior boundaries of the green outlined area.
Fig. 7.4. Dipole source solutions (and surrounding CEs) obtained for averaged (n = 64) right anterior temporal lobe spikes using (left) a non-individualized FEM volume conductor created from the MNI averaged brain dataset and (right) a BEM volume conductor created from patient’s own MRI. LFF = 1 Hz. Valid dipole source localizations obtained with both FEM ($x = 42.2$ mm, $y = 37.6$ mm, $z = 11.3$ mm) and BEM ($x = 41.3$ mm, $y = 32.5$ mm, $z = 17.5$ mm) forward models (compare with true intracranial localization, Fig. 7.3).
Fig. 7.5. Distributed source modeling of averaged (n = 64) right anterior temporal lobe spikes using sLORETA. Same EEG data used for dipole mapping in Fig. 7.4. LFF = 1 Hz. Volume conductor = BEM; cortical subspace constraint = fixed normal sources, 20 mm extended patch. The distributed source solution had a localized maximum value at $x = 37.0$ mm, $y = 31.3$ mm, $z = 27.6$ mm; $V = 98.29\%$. Sources shown on high resolution cortical reconstruction of patient’s own brain MRI. (A) Distributed modeling solution displayed with cutoff threshold set at 50%: solutions with smaller explained field percentages (as a percentage of the largest current) excluded from display. (B) Setting cutoff threshold to 75% removes “ghost” sources but the remaining distributed source solution is smaller in extent than the true intracranial cortical source.
Fig. 7.6. Dipole source solutions for individual right anterior temporal spikes; BEM volume conductor. Columns, from left to right, show solutions for spikes 1-16, 17-32, 33-48 and 49-64. (A) LFF = 1 Hz. (B) LFF = 3 Hz. Use of the individualized BEM volume conductor led to solutions that were less scattered, more reliable and more often valid than those obtained with the FEM forward model ($p = 0.017$ for LFF = 1 Hz, $p = 0.019$ for LFF = 3 Hz; compare with Supplementary Fig. 7.S4). Nonetheless, some spikes were associated with strikingly incorrect dipole source localizations or orientations, despite the intracranial similarity of all 64 spikes. The scatter of dipole sources was decreased and the number of valid solutions increased ($p = 0.008$) with the 3 Hz LFF.
Fig. 7.7. Goodness-of-fit (% explained variance, $V$) as a predictor of valid dipole source localization and orientation for individual EEG spikes. Volume conductor = BEM. With LFF = 1 Hz, 36.4% of dipole sources with $V > 90\%$ were physiologically valid, compared with 33.3% of dipole sources with $V \leq 90\%$ (left); with LFF = 3 Hz, 65.7% of dipole sources with $V > 90\%$ were physiologically valid, compared with 44.8% of dipole sources with $V \leq 90\%$ (right).
Fig. 7.8. Dipole source solutions obtained with modeling performed at the midpoint of the negative spike upswing (determined as the timepoint: \( \frac{1}{2} \times \) maximum mean global field power; \( t = -16 \text{ ms} \). BEM volume conductor. LFF = 1 Hz. (A) Valid source solution obtained with dipole mapping performed on grand average of all 64 spikes \( (x = 43.5 \text{ mm}, y = 29.7 \text{ mm}, z = 18.6 \text{ mm}; \text{CE} = 0.1 \text{ ml}; V = 91.85\%) \). SNR (6.4) and dipole amplitude (300.05 \( \mu \text{Amm} \)) values approximately 50% lower than with modeling performed at spike peak (Table 7.1). (B) Reliability and validity of dipole source solutions obtained for individual spikes was poor. Only source solutions with \( V > 80\% \) shown (yellow \( V > 80-90\% \), orange \( V > 90-95\% \)).
Fig. 7.9. Effects of spike averaging on dipole source localization and orientation for right anterior temporal EEG spikes, BEM volume conductor, LFF = 1 Hz (left) and LFF = 3 Hz (right). LFF setting of 3 Hz associated with significantly greater number of valid dipole sources for individual spikes ($p = 0.008$) and a trend toward a greater proportion of valid solutions after spike averaging. With LFF = 1 Hz, validity of source solutions was improved after averaging 4 ($p < 0.005$) or more spikes. With LFF = 3 Hz, validity of source solutions was improved after averaging 4 ($p < 0.01$) spikes.
Figure 10. Dipole source solutions for averages of 8 right anterior temporal spikes (spikes 1-8, 9-16...57-64), BEM volume conductor. (A) LFF = 1 Hz. Dipole source goodness-of-fit levels indicated in color (inset); orange $V > 95\%$, yellow $V > 90-95\%$, cyan $V > 85-90\%$. (B) LFF = 3 Hz. Dipole source goodness-of-fit levels indicated in color (inset); orange $V > 95\%$, yellow $V > 90-95\%$, green $V > 80-85\%$. 
Fig. 7.11. (A) Averaged left anterior temporal lobe spike waveform in same patient; data obtained from same stereoelectroencephalographic recordings described in Fig. 7.1. Spikes averaged on intracranial contact with maximal peak amplitude (LTA1; n = 48). The neocortical spike localization is associated with an anterior temporal scalp EEG spike field maximal at F7, F9, Sp1. Sensitivity, filters, montage as in Fig. 7.1. (B) Localization of left anterior temporal spike maximum on patient’s pre-operative high resolution MRI (green crosshairs; localization obtained through MRI co-registration as described in Fig. 7.3). (C) Dipole source solution obtained for averaged (n = 48) left anterior temporal lobe spikes. Volume conductor = BEM. LFF = 1 Hz.
Supplementary data to: EEG source imaging of anterior temporal lobe spikes: validity and reliability

sLORETA modeling of individual spikes

Supplementary Fig. 7.S6 shows representative results of sLORETA performed on spikes 8 and 12, the former an example of a spike poorly localized by dipole mapping, the latter an example of a spike well localized by dipole mapping. For spike 8, sLORETA returned mislocalized deep midline source maxima using both rotating sources ($x = -2.6$ mm, $y = 7.6$ mm, $z = 24.2$ mm) and fixed sources with no extension ($x = -9.7$ mm, $y = 8.3$ mm, $z = 30.8$ mm; not shown), similar to the source localization obtained with dipole mapping ($x = -6.5$ mm, $y = 9.5$ mm, $z = 39.8$ mm). For the same spike, using a solution subspace of fixed sources extended over 20 mm, sLORETA mislocalized the distributed source maximum to the right frontal lobe ($x = 14.1$ mm, $y = 62.0$ mm, $z = 37.6$ mm). For spike 12, sLORETA source maxima were slightly closer to the true intracranial source in the $x$ plane, but slightly further away in the $y$ and $z$ planes ($x = 38.8$ mm, $y = 29.6$ mm, $z = 21.2$ mm (rotating sources), $x = 39.8$ mm, $y = 31.2$ mm, $z = 22.6$ mm (fixed sources, no extension; not shown), $x = 42.6$ mm, $y = 27.9$ mm, $z = 26.9$ mm (fixed sources, 20 mm extension)) than the dipole source solution ($x = 33.2$ mm, $y = 33.5$ mm, $z = 17.5$ mm).

Spike peak versus mid upswing modeling

The best time point to select along the course of a spike deflection for ESI is a matter of ongoing debate. Many authors have suggested that modeling should be performed at the mid upswing of a spike, based on the hypothesis that propagation from an initial zone of spike generation is less likely to have occurred during the early portion of an extracranially recorded spike, and yet the spike amplitude at mid upswing may provide a SNR high enough for source modeling (Ebersole, 2000; Lantz et al., 2003; Ray et al., 2007; Ebersole and Hawes-Ebersole, 2008).
However, the SNR at the mid upswing is in general significantly lower than at the spike peak and clinical data exists to suggest that relinquishing the SNR benefits of modeling at the spike peak may compromise the reliability of ESI (Merlet and Gotman, 1999; Bast et al., 2006; Wang et al., 2011).

In this study, given that it was known at the outset (from intracranial recordings) that the spikes to be analyzed were not propagated from a cortical source different from the focus of maximal spike amplitude, it would not have been logical to concentrate modeling on any time point other than the spike peak, where one could derive maximal SNR benefit. For purposes of comparison, however, modeling was also performed at the mid upswing and the results demonstrated the detrimental effects that may occur when compromising SNR by modeling at the mid upswing of individual spikes. Mean SNR and mean $V$ were markedly reduced by modeling individual spikes at the mid upswing. More importantly, the scatter of dipole sources increased substantially (i.e. reliability decreased) and the proportion of physiologically valid source localizations decreased.

Notwithstanding, modeling performed at the mid upswing of the grand averaged spike, although associated with a lower SNR, lower goodness-of-fit and larger CE than that obtained with modeling at the spike peak, actually provided a physiologically valid source localization (with the BEM volume conductor) similar to that obtained with modeling the grand average at the spike peak. (Using the FEM volume conductor, the source solution was displaced posteriorly to the superficial mid temporal region and associated with a larger CE (6.0 ml; not shown)). Nevertheless, no benefits were attained with modeling performed at the mid upswing.

As a recommendation – given the clear benefits in terms of SNR associated with modeling performed at the spike peak – it would seem that ESI should be routinely performed at the spike peak, rather than at the mid upswing of the spike. The benefits of ESI performed at the mid upswing are mainly theoretical and to date unsupported by empirical evidence, which can only be obtained by direct comparison of the source localization results obtained with existing methods.
ESI techniques against the true cortical spike fields identified with simultaneous intracranial EEG recording, as was done in this study. It is perhaps not unreasonable to consider modeling at both the mid upswing and the spike peak and to compare the obtained results, however, in the absence of visual evidence of spike waveform propagation in the scalp EEG, the compromises in source imaging reliability and localization validity associated with mid upswing modeling would appear to outweigh any theoretical benefit.

_Averaged versus individual spikes; LFF effects; FEM volume conductor_

Using the FEM volume conductor and LFF = 3 Hz the proportion of valid dipole source solutions was significantly increased after averaging 4 or 8 spikes (both \( p < 0.05 \)) as compared with the analyses performed on single spikes. With LFF = 1 Hz, there was a trend toward a greater proportion of valid solutions after averaging 8 spikes (\( p = 0.077 \)).

The 3 Hz LFF was associated with significantly more valid source solutions than the 1 Hz LFF for averages of 2 and 4 spikes (\( p < 0.05 \)). However, the validity of solutions obtained after averaging 8 spikes did not differ significantly between LFF settings.

_Averaged spikes; LFF effects; FEM versus BEM volume conductors_

At the 1 Hz LFF setting, the BEM volume conductor was associated with significantly more valid source solutions than the FEM volume conductor after averaging 2 or 4 spikes (\( p < 0.05 \) and \( p < 0.01 \), respectively). However, the proportion of valid solutions did not differ significantly between the two forward models after averaging 8 spikes. With LFF = 3 Hz, there was a trend toward a greater proportion of valid solutions with the BEM as compared to FEM volume conductor after averaging 2 spikes, but this did not reach significance (\( p = 0.060 \)), and there were no differences between the two forward models after averaging 4 or more spikes.
Supplementary Table 7.S1. CEs of right anterior temporal EEG spikes; individual (n=64) and averaged (2^x, x=1,2,3...6) spikes, BEM and FEM volume conductors, different LFFs (1 Hz, 3 Hz, 6 Hz).

<table>
<thead>
<tr>
<th>Confidence Ellipsoid Volumes (ml) – EEG</th>
<th>LFF 1 Hz</th>
<th>LFF 3 Hz</th>
<th>LFF 6 Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ind. Spikes (n=64)</td>
<td>BEM 1294.9 ± 7014</td>
<td>BEM 228.6 ± 795</td>
<td>BEM 140.3 ± 357</td>
</tr>
<tr>
<td></td>
<td>FEM 959.4 ± 1945</td>
<td>FEM 482.3 ± 1133</td>
<td>FEM 1862.4 ± 7955</td>
</tr>
<tr>
<td>Av. 2 spikes (n=32)</td>
<td>BEM 94.22 ± 185</td>
<td>BEM 30.54 ± 50.2</td>
<td>BEM 23.85 ± 35.8</td>
</tr>
<tr>
<td></td>
<td>FEM 246.8 ± 378</td>
<td>FEM 83.55 ± 167</td>
<td>FEM 1038.9 ± 4940</td>
</tr>
<tr>
<td>Av. 4 spikes (n=16)</td>
<td>BEM 12.58 ± 13.0</td>
<td>BEM 8.69 ± 14.0</td>
<td>BEM 7.06 ± 11.5</td>
</tr>
<tr>
<td></td>
<td>FEM 286.8 ± 801</td>
<td>FEM 31.94 ± 52.2</td>
<td>FEM 31.87 ± 38.1</td>
</tr>
<tr>
<td>Av. 8 spikes (n=8)</td>
<td>BEM 9.49 ± 16.4</td>
<td>BEM 2.29 ± 4.3</td>
<td>BEM 3.88 ± 8.9</td>
</tr>
<tr>
<td></td>
<td>FEM 24.29 ± 39.1</td>
<td>FEM 4.71 ± 4.9</td>
<td>FEM 6.35 ± 2.9</td>
</tr>
<tr>
<td>Av. 16 spikes (n=4)</td>
<td>BEM 0.93 ± 1.0</td>
<td>BEM 1.0 ± 1.2</td>
<td>BEM 0.65 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>FEM 18.05 ± 13.2</td>
<td>FEM 2.3 ± 1.2</td>
<td>FEM 4.25 ± 5.1</td>
</tr>
<tr>
<td>Av. 32 spikes (n=2)</td>
<td>BEM 0.4 ± 0.3</td>
<td>BEM 0.15 ± 0.1</td>
<td>BEM 2.5 ± 2.5</td>
</tr>
<tr>
<td></td>
<td>FEM 0.75 ± 0.4</td>
<td>FEM 0.1 ± 0.1</td>
<td>FEM 0.05 ± 0.1</td>
</tr>
<tr>
<td>Av. 64 spikes (n=1)</td>
<td>BEM 0.05 ± 0.1</td>
<td>BEM 0.1 ± 0.1</td>
<td>BEM 1.45 ± 1.6</td>
</tr>
</tbody>
</table>

Av.=average, BEM=boundary element method, FEM=finite element interpolated method, Ind.=individual, LFF=low frequency filter
Supplementary Figure 7.S1B

Fig. 7.S1. Stereoelectroencephalographic recordings of individual right anterior temporal spikes 1, 2, 3...16 (from the 64 spikes averaged in Fig. 7.1). (A) Intracranial EEG. (B) Simultaneous scalp EEG. Common average reference and filters as in Fig. 7.1.
Supplementary Figure 7.S2A
Supplementary Figure 7.S2B

Fig. 7.S2. Stereoelectroencephalographic recordings of individual right anterior temporal spikes 33,34,35...48 (from the 64 spikes averaged in Fig. 7.1). (A) Intracranial EEG. (B) Simultaneous scalp EEG. Common average reference and filters as in Fig.7.1.
Supplementary Figure 7.S3B

Fig. 7.S3. Stereoelectroencephalographic recordings of individual right anterior temporal spikes 49,50,51...64 (from the 64 spikes averaged in Fig. 7.1). (A) Intracranial EEG. (B) Simultaneous scalp EEG. Common average reference and filters as in Fig. 7.1.
Fig. 7.S4. Dipole source solutions for individual right anterior temporal spikes; FEM volume conductor. Columns, from left to right, show solutions for spikes 1-16, 17-32, 33-48 and 49-64. (A) LFF = 1 Hz. (B) LFF = 3 Hz. Scattered solutions clustered around right anterior temporal lobe, but reliability and intralobar validity with respect to both localization and orientation was poor with single spike analysis (despite the intracranial similarity of each spike; compare with Figs. 7.1, 7.2, 7.S1-7.S3). The scatter of dipole sources was decreased and the number of valid solutions increased ($p = 0.017$) with the 3 Hz LFF.
Fig. 7.S5. Effects of dipole component regularization and EEG data preprocessing with principal and independent component analysis (PCA/ICA) on source localization solutions of four individual spikes, whose source solutions ranged from relatively well localized without preprocessing to very poorly localized without preprocessing (selected from the first group of 16 spikes, Supplementary Fig. 7.S1). Volume conductor = BEM; sources shown on high resolution cortical reconstruction of patient’s own brain MRI. Regularization alone improved slightly the localization of the dipole source for spike 12, but worsened the source solutions of the other three spikes. PCA/ICA combined with regularization worsened the source localization of all four spikes. PCA/ICA alone was associated with source solutions that differed little from those obtained without data preprocessing.
Fig. 7.S6. Distributed source modeling of two individual right anterior temporal lobe spikes using sLORETA. LFF = 1 Hz. Volume conductor = BEM; cortical solution subspace constraint with rotating sources, no extension (top 2 rows) or fixed normal sources in a 20 mm extended patch (bottom 2 rows). Source solutions shown on high resolution cortical reconstruction of patient’s own brain MRI. Cutoff threshold set at 75%: solutions with smaller explained field percentages (as a percentage of the largest current) excluded from display. (A) Spike 8. Comparison of dipole source solution (left) with sLORETA results showed similarly invalid deep midline solutions using both methods for this anterior temporal spike. (B) Spike 12. Comparison of dipole source solution (left) with sLORETA results showed similar valid anterior temporal maximal solutions using both methods (although the fixed normal sources in an extended cortical patch sLORETA solution subspace produced a separate orbitofrontal “ghost” source for this anterior temporal spike).
Supplementary Figure 7.S7

**Fig. 7.S7.** Signal to noise ratio (SNR) as a predictor of valid dipole source localization for individual right anterior temporal EEG spikes. LFF = 1 Hz. Volume conductor = BEM. SNR for individual spikes was not a good predictor of dipole source proximity to true intracranial localization in x-plane (dotted vertical line, 47.5 mm, *top*) or y-plane (dotted vertical line, 34.6 mm, *bottom*).
Supplementary Figure 7.S8

EEG dipole source localizations, x, y, and z planes, BEM

LFF 1 Hz

LFF 3 Hz

LFF 6 Hz
**Fig. 7.8.** Effects of spike averaging and LFF setting on EEG dipole source localizations in $x$ (red diamonds), $y$ (blue triangles) and $z$ (grey circles) planes. Horizontal dotted lines indicate true intracranial source localization in $x$ (red, 47.5 mm), $y$ (blue, 34.6 mm) and $z$ (grey, 18.9 mm) planes. Volume conductor = BEM. LFF settings of 3 Hz and 6 Hz reduced scatter (improved reliability) of individual spike dipole sources compared with LFF = 1 Hz. Spike averaging improved reliability and validity of source solutions at all LFF settings. Dipole source solutions for the grand average of 64 spikes closest to true localization with LFF settings of 1 Hz and 3 Hz. Ind. = individual, Ave. 2 = average of 2 spikes (1-2,3-4...63-64), Ave. 4 = average of 4 spikes (1-4,5-8...61-64), Ave. 8 = average of 8 spikes (1-8,9-16...57-64), Ave. 16 = average of 16 spikes (1-16, 17-32...49-64), Ave. 32 = average of 32 spikes (1-32,33-64), Ave. 64 = average of all 64 spikes.
Supplementary Figure 7.S9

Fig. 7.S9. Dipole source solutions for individual left anterior temporal spikes; BEM volume conductor. Columns, from left to right, show solutions for spikes 1-16, 17-32 and 33-48. (A) LFF = 1 Hz. (B) LFF = 3 Hz. As with the right anterior temporal spikes, solutions appeared qualitatively less scattered (more reliable) and more often valid with the 3 Hz LFF. Many spikes were associated with markedly incorrect dipole source localizations or orientations despite intracranial similarity of all 48 spikes.
Supplementary Figure 7.S10

**Fig. 7.S10.** Dipole source solutions for averages of 8 left anterior temporal spikes (spikes 1-8, 9-16...41-48) with LFF = 1 Hz (*left*) and LFF = 3 Hz (*right*). Volume conductor = BEM. As with the right anterior temporal spikes, reliability and validity of source solutions was improved after spike averaging, especially with LFF = 3 Hz. Source solutions for grand average of 48 spikes essentially identical with both LFF settings (*insets*).
Supplementary Figure 7.S11

Fig. 7.S11. Averaged (n = 18) left lateral (mid) temporal spike scalp EEG waveform (left). Spikes averaged on simultaneously acquired intracranial EEG spike peak (see Fig. 9 in Wennberg et al., 2011). Lateral (mid) temporal scalp EEG field maximal at T3, T9. Data obtained from same stereoelectroencephalographic recordings described in Fig. 7.1. Sensitivity, filters, montage as in Fig. 7.1. Voltage topographic plot of averaged spike and dipole source localizations (right) for individual spikes (yellow and orange) and grand averaged spike (n = 18; red), modeled at spike peak (t = -2 ms; interval for source localization -50 ms to +4 ms). Dipole source goodness-of-fit levels for single spike source solutions indicated in color; orange $V > 95\%$, yellow $V > 90-95\%$ (3/18 individual spike source solutions with $V < 90\%$ not shown). Volume conductor = BEM. LFF = 3 Hz.
Chapter Eight

Reliability of MEG source imaging of anterior temporal spikes:

Analysis of an intracranially characterized spike focus

Previously published as:

Wennberg, R. and Cheyne, D.
Reliability of MEG source imaging of anterior temporal spikes: analysis of an intracranially characterized spike focus.
Abstract

Objective: To assess the reliability of MEG source imaging (MSI) of anterior temporal spikes through detailed analysis of the localization and orientation of source solutions obtained for a large number of spikes that were separately confirmed by intracranial EEG to be focally generated within a single, well-characterized spike focus.

Methods: MSI was performed on 64 identical right anterior temporal spikes from an anterolateral temporal neocortical spike focus. The effects of different volume conductors (sphere and realistic head model), removal of noise with low frequency filters (LFFs) and averaging multiple spikes were assessed in terms of the reliability of the source solutions.

Results: MSI of single spikes resulted in scattered dipole source solutions that showed reasonable reliability for localization at the lobar level, but only for solutions with a goodness-of-fit exceeding 80% using a LFF of 3 Hz. Reliability at a finer level of intralobar localization was limited. Spike averaging significantly improved the reliability of source solutions and averaging 8 or more spikes reduced dependency on goodness-of-fit and data filtering.

Conclusions: MSI performed on topographically identical individual spikes from an intracranially defined classical anterior temporal lobe spike focus was limited by low reliability (i.e., scattered source solutions) in terms of fine, sublobar localization within the ipsilateral temporal lobe. Spike averaging significantly improved reliability.

Significance: MSI performed on individual anterior temporal spikes is limited by low reliability. Reduction of background noise through spike averaging significantly improves the reliability of MSI solutions.
8.1. Introduction

MEG source imaging, or MSI, has gained increased use as an adjunctive technique for
the localization of epileptogenic brain tissue in the presurgical investigation of patients with
intractable epilepsy (Ebersole, 1997; Knowlton et al., 1997; Baumgartner et al., 2000; Mamela
et al., 2002; Pataaraia et al., 2002; Barkley and Baumgartner, 2003; Stefan et al., 2003; Fischer et
al., 2005; Paulini et al., 2007; Rampp and Stefan, 2007; Lam et al., 2008; Agirre-Arrizubieta et
al., 2009).

The validity of the source localization results obtained using MSI has typically been
assessed by comparisons with postsurgical outcomes (Sutherling et al., 1988; Nakasato et al.,
1994; Wheless et al., 1999; Iwasaki et al., 2002; Mamela et al., 2002; Assaf et al., 2004; Bast et
al., 2004; Genow et al., 2004; Fischer et al., 2005; Papinicolaou et al., 2005; Pataaraia et al., 2005;
Knowlton et al., 2006; Oishi et al., 2006; Paulini et al., 2007; RamachandranNair et al., 2007;
Kaiboriboon et al., 2010), structural lesions visible on brain MRI (Nakasato et al., 1994;
Knowlton et al., 1997; Diekmann et al., 1998; Otsubo et al., 2001; Bast et al., 2004), regions of
metabolic abnormalities demonstrated using other functional imaging techniques such as PET and
SPECT (Stefan et al., 1992; Lamusuo et al., 1999; Sakamoto et al., 2003), localization of ictal
onset zones using intracranial EEG recordings obtained later during patients’ investigations
(Sutherling et al., 1988; Stefan et al., 1992; Knowlton et al., 1997; Minassian et al., 1999; Otsubo
et al., 1999; Hisada et al., 2001; Mamela et al., 2002; Assaf et al., 2004; Knowlton et al., 2006;
Oishi et al., 2006) and occasionally interictal intracranial EEG findings obtained during later
chronic or acute electrocorticography investigations (Sutherling et al., 1988; Nakasato et al.,
1994; Ko et al., 1998; Leijten et al., 2003; Bast et al., 2004; Agirre-Arrizubieta et al., 2009;
Huiskamp et al., 2010).

Most of these methods have limitations with respect to validating the source localization
results obtained using MEG, including (a) the fact that the interictal spikes modeled with MSI are
frequently recorded at a distance from the seizure generating regions of the brain, especially for
mesial temporal lobe epilepsy (MTLE), where seizure freedom after anteromesial temporal resection does not depend on removal of the neocortical areas responsible for generation of the extracranially recorded interictal spikes (Cendes et al., 1993; Tran et al., 1995; Wennberg et al., 1997a,b, 2011; Knowlton et al., 2006; Wennberg, 2006), (b) the longstanding observation that interictal spikes are frequently recorded at a distance from structural lesions and do not necessarily show a fine degree of overlap with hypometabolic lesions visualized with other functional imaging techniques (Talairach and Bancaud, 1966; Sakamoto et al., 2003; Zumsteg et al., 2005; Bagshaw et al., 2006), and (c) that the comparison of interictal spikes modeled with MSI and ictal intracranial EEG recordings is a method comparing two different entities, which are in a broad sense related but not necessarily bound to overlap closely at a fine level of localization in the brain (Wennberg et al., 2011).

The reliability of the results obtained using MSI performed on identical spikes has not been a topic of systematic research. Rare simultaneous MEG and intracranial EEG recordings have concentrated primarily on determining the sensitivity of MEG to detect intracranially recorded spikes (Mikuni et al., 1997; Oishi et al., 2002; Shigeto et al., 2002), as have studies that have directly compared MSI results with interictal spikes recorded during subsequent electrocorticographic recordings (Agirre-Arrizubieta et al., 2009; Huiskamp et al., 2010). These investigations have not directly examined the degree to which MSI may provide a reliable source solution for a given spike generated from a single spike focus, i.e., the degree to which MSI may be expected to show a consistent result whenever applied to a spike that corresponds to a well-characterized focal cortical source, as confirmed by intracranial recordings in the same patient.

It has become common clinical practice to consider clusters of MEG dipole sources as a localizing marker extended in space, possibly representing the overall extent of epileptogenic cortex responsible for giving rise to similar appearing spikes recorded with MEG (Otsubo et al., 2001; Mamelak et al., 2002; Bast et al., 2004; Oishi et al., 2006; RamachandranNair et al., 2007). This concept has frequently enabled useful localization at the lobar level (Otsubo et al., 2001;
Mamelak et al., 2002; Pataaraia et al., 2002; Stefan et al., 2003; Oishi et al., 2006; Paulini et al., 2007; Ramachandran Nair et al., 2007), however, the underlying premise that the extent of the source solution cluster represents the extent of the epileptogenic cortex comprising a spike focus in the brain has not been fully tested. The hypothesis that dipole source clusters represent an extended region of cortex capable of generating independent spikes – that appear topographically similar extracranially – is based on the concept that such spikes may be generated from anywhere within a brain region comprising many square centimeters, with no single focal maximum to the true intracranial spike source. However, a priori, another equally plausible explanation for clusters of scattered dipole sources may simply be spatial inaccuracy of the noninvasive source localization methodology – spikes with the same extracranial topographic fields might actually have a consistent focal cortical source maximum that may not be reliably modeled, from one spike to the next, by existing MSI techniques (Bast et al., 2004).

In an attempt to shed further light on this issue we present here a detailed analysis of MSI performed on a collection of identical spikes known from intracranial EEG recordings to be generated within a consistently localized brain region situated in the anterolateral temporal neocortex. We hypothesized that, in this particular well-characterized case of a focal spike generator, a reliable source localization technique should return an identical solution for each spike analyzed. Relatedly, scattered source solutions would not reflect an extended region of epileptogenic cortex responsible for spike generation but rather limitations in the spatial accuracy of the source localization technique.

8.2. Methods

MEG and EEG source localization was performed on data acquired during the course of presurgical clinical investigations in a patient suffering from intractable MTLE. Some data from this patient’s investigations have been presented previously (patient M5 in Wennberg et al., 2011). Brain MRI showed right hippocampal sclerosis; noninvasive scalp EEG-video monitoring
demonstrated bilateral independent anterior and mid temporal spikes and ictal recordings were inconclusive as to lateralization. A simultaneous MEG/EEG study confirmed the presence of bilateral right greater than left temporal lobe spikes, and, one week later, the patient underwent stereoelectroencephalographic-video monitoring for definitive localization of ictal onsets: clinical seizures were found to arise independently from both mesial temporal regions, but with a right-sided predominance at a ratio greater than 9:1. A right anteromesial temporal resection has resulted in an Engel Class IC outcome.

The simultaneous MEG/EEG recording was acquired using a 151-channel whole head CTF MEG system (Port Coquitlam, BC, Canada) including 19 standard 10-20 scalp EEG channels. Fifteen separate 2-minute recording segments were obtained; recording bandpass 1-210 Hz, fourth order gradient, sampling frequency 625 Hz.

The stereoelectroencephalographic recordings in this patient revealed six distinct, independent neocortical temporal lobe spike foci (right anterolateral, right mesiobasal, left anterolateral, left anterobasolateral with anterior to posterior neocortical propagation, left lateral, and left mesiobasal), which have been extensively characterized in terms of their topographies and locations in a previous study (Wennberg et al., 2011). In this study we chose to analyze in more detail the right anterolateral spike focus because (a) it represents an archetypal example of the classical anterior temporal lobe spike pattern seen in MTLE, and (b) abundant spikes from this right anterior temporal focus were recorded during the MEG/EEG investigation in numbers sufficient to permit investigation with respect to the reliability of source localization results.

Fig. 8.1 shows representative examples of the intracranial and scalp EEG fields of the right anterior temporal lobe spike focus as documented during the patient’s stereoelectroencephalographic investigation. The spike generator was localized entirely to the anterolateral temporal neocortex, with no evidence of propagation elsewhere in the temporal lobe (Wennberg et al., 2011). The intracranial distribution of the electrical field of spikes generated within this focus is depicted in full detail in (Wennberg and Cheyne, 2014b). Descriptively, the
surface negative anterolateral temporal neocortical spike peak that appears with maximal
amplitude at subdural contact RTA2 shows a consistent amplitude decrement of more than 50%
at the subdural contacts situated 1 cm anteromedially and 1 cm posterolaterally to RTA2, with the
spike potential essentially isoelectric at the subdural contact situated 2 cm posterolaterally to the
peak maximum at RTA2 (Fig. 8.1). The depth electrode contacts situated in the subcortical
temporal white matter posterior to the cortical spike source show a synchronous, low amplitude
waveform, inverted in polarity, representing the volume conducted electropositive field of the
“opposite” side of the anterior temporal cortical dipole layer, as is typical for classical anterior
temporal lobe spike generators in patients with MTLE (Wennberg, 2010a; Wennberg et al.,
2011). Quantitatively, the mean maximal peak to peak amplitudes at the different intracranial
electrode contacts, as measured from the 142 representative right anterolateral temporal spikes
presented in (Wennberg et al., 2011), were: RTA1 = 945 (± 231) µV; RTA2 = 2,681 (± 652) µV;
RTA3 = 1,219 (± 441) µV; RTA4 = 378 (± 209) µV; RTD4 = 520 (± 210) µV (the waveform
inverted in polarity at the latter site). Mean peak to peak amplitudes were below 225 µV at all
other intracranial electrode contacts. Supplementary Fig. 8.S1 shows the corresponding mean
spike amplitude ratios at the different intracranial electrode contacts (as a percentage of the
maximum peak to peak amplitude at RTA2): RTA1 = 35% (± 7%); RTA3 = 44% (± 10%); RTA4
= 14% (± 7%); RTD4 = 19% (± 8%). Spike amplitude ratios were ≤ 9% at all other intracranial
electrode contacts (Supplementary Fig. 8.S1).

As an initial test for reproducibility of the MSI results applicable to the reliability of
source modeling solutions, a separate temporal lobe MEG spike focus (the ipsilateral right
mesiobasal focus identified in the same patient (Wennberg et al., 2011)) was also analyzed
qualitatively. This focus was not studied to the same extent, as fewer spikes were available to
assess reliability. Furthermore, the waveforms were of much lower amplitude (especially in EEG;
Wennberg et al., 2011) and thus more difficult to identify with certainty – in the absence of
simultaneous intracranial EEG recording – as arising from the same mesiobasal temporal
neocortical spike focus delineated during the stereoelectroencephalographic investigation. Analysis of this mesiobasal spike focus was also included because of its comparatively advantageous field orientation (with little radial component) for MEG signal detection.

8.2.1. MEG spike selection

Sixty-four right anterior temporal lobe spikes were selected for subsequent analysis from a total of 108 similar spikes recorded during the MEG/EEG investigation. The MEG spikes were manually selected after careful visual examination of the simultaneous EEG spike waveform morphology and associated surface voltage topographic field to ensure all spikes represented the same right anterolateral temporal neocortical focus described in (Wennberg et al., 2011; Wennberg and Cheyne, 2014b). MEG spikes were averaged using CURRY 6 (Abbotsford, Victoria, Australia).

A total of 32 presumptive right mesiobasal temporal spikes were captured during the MEG/EEG investigation and these were selected for comparative analysis.

8.2.2. Source localization

Source localization of individual and averaged spikes was performed using CURRY 6 (Abbotsford, Victoria, Australia). Spike epochs were generated using a time window from -750 to +250 ms relative to the spike peak (which occurred simultaneously in the MEG and EEG recordings). The interval selected for source localization analysis was from -40 to +12.8 ms, representing the time from spike onset to just after peak (t = 4.8 ms) latency (for the mesiobasal spikes the interval was –19.2 to +32 ms, peak at t = 17.6 ms). Given the intracranial EEG evidence that the spikes were neither propagated from nor to other regions in the temporal lobe (Fig. 1 and Wennberg et al., 2011), modeling was performed on the spike peaks. Noise level was estimated as the variance of the data in the signal from -750.4 to -251.2 ms before each individual
or averaged spike. The HFF setting for source localization was 30 Hz. Three different LFF settings were tested: 1 Hz, 3 Hz and 6 Hz.

To further ensure spikes identified during the MEG/EEG study represented examples of the same anterior temporal lobe spike focus previously described in (Wennberg et al., 2011; Wennberg and Cheyne, 2014b), EEG dipole source localization of the averaged (n = 64) spike was performed using the 19 10-20 channels available from the MEG/EEG study. The localization results were then compared with an identical analysis performed (as described in Wennberg and Cheyne, 2014b) on the averaged (n = 64) spike from the stereoelectroencephalographic study, limited to the same 19 electrodes that were available in the MEG/EEG investigation (i.e., excluding F9/10, T9/10, P9/10 and Sp1/2 from the calculations). The reliability and validity of source modeling performed on individual EEG spikes from this anterolateral temporal neocortical spike focus are presented separately in (Wennberg and Cheyne, 2014b).

As has been previously described (Ebersole and Ebersole, 2010), MEG dipole source solutions were usually localized posterior to EEG dipole source solutions (and to the known intracranial anterior temporal cortical generator). Because of this yet unexplained phenomenon (Ebersole and Ebersole, 2010) MEG dipole source localization validity was not assessed by comparison against the known intracranial cortical generator. Instead, localizations were deemed “valid” for dipole sources situated within 1 cm on either side, in the x, y and z planes, of the grand average MEG source solutions, accepting the consistent posterior displacement of MEG sources away from the true intracranial anterior temporal cortical source. Dipole vectors that projected anteriorly or anterolaterally through temporal neocortex were deemed valid.

The comparative effects of the different LFF settings on the reliability and validity of source localization results were analyzed quantitatively using the non-parametric Mann-Whitney U test, with each spike (or averaged spike) given a ranking of 0, 1, 2 or 3, where 0 = localization and orientation both incorrect, 1 = localization incorrect, orientation correct, 2 = localization correct, orientation incorrect, 3 = localization and orientation both correct. Correct (i.e., valid, as
defined above) localization alone was ranked higher than correct orientation alone given the
greater clinical utility of accurate localization. The statistical analyses were restricted to results
obtained using the sphere volume conductor and were not performed on averages of 16 or more
spikes (i.e., where total $n < 5$).

8.2.3. Forward models

The effects on MEG source localization of different forward models (volume conductors;
Fuchs et al., 2001, 2007) were assessed by comparing MSI results obtained using either: (a) a
spherical model calculated from the Montreal Neurological Institute (MNI) averaged brain MRI
dataset, or (b) an individualized model created from the patient’s own MRI using the boundary
element method (BEM). Both models were created within the CURRY 6 software platform.

8.2.4. Inverse models

Dipole mapping was performed using the fixed coherent dipole modeling algorithm in
CURRY 6, corresponding to the classical equivalent current dipole model. Confidence ellipsoids
(CEs) shown surrounding dipole solutions indicate regions within which changes in forward
calculated data would be below noise compared to the forward calculated data obtained for the
best-fit dipole location (Fuchs et al., 2004).

Distributed source modeling was performed using sLORETA (Pascual-Marqui, 2002;
Wagner et al., 2004). The effects of different solution subspace choices on localization were
examined by comparing the results obtained using (a) a cortically constrained subspace with
rotating sources and (b) a cortically constrained subspace with fixed normal sources, extended
over a 20 mm patch (Plummer et al., 2010a,b).

8.2.5. Spike averaging
To assess the effects on source localization of spike averaging, solutions obtained from modeling individual spikes were compared to solutions obtained from modeling averages of 2, 4, 8, 16, 32 and the grand average of 64 spikes. Spikes were averaged in progressively larger groups moving from left to right on the number line (e.g., averages of 2 spikes comprised spikes 1-2, 3-4, ... 63-64, averages of 4 spikes comprised spikes 1-4, 5-8, ... 61-64, and so on).

8.2.6. Data preprocessing

For the grand average of spikes, the effects of regularization on the dipole modeling algorithm were assessed, using a weighting (regularization parameter) of $\lambda = 1.0$ (eliminating dipole components with a contribution to the forward-fit signal < 1.0 of the signal to noise ratio (SNR) at a given time point; Michel et al., 2004; Plummer et al., 2007, 2010a,b).

The effects of including the 19 channel EEG data in the source localization process and the effects of preprocessing the MEG data using principal component analysis (PCA) and independent component analysis (ICA) were also analyzed. In the latter de-noising procedure, PCA was first performed on the data to identify orthogonal (uncorrelated) components, which then underwent ICA to identify statistically independent signal components. Mean global field orthogonal signal components of spikes with a SNR > 1.0 identified by PCA underwent ICA (Onton et al., 2006; Plummer et al., 2007, 2010a,b).

8.3. Results

Fig. 8.2 shows the simultaneously acquired MEG and EEG spike waveforms for the grand average of all 64 spikes, along with their topographic maps and dipole source solutions.

Fig. 8.3 shows that EEG source imaging (ESI) performed on the 19 channel EEG data acquired simultaneously with the MEG recording provided a source solution very similar to that obtained when modeling data acquired from the same 19 electrode positions during the subsequent stereoelectroencephalographic recording, indicating that the spikes selected for study
in the MEG/EEG investigation represent the same spike focus characterized by intracranial EEG (Wennberg et al., 2011; Wennberg and Cheyne, 2014b).

Fig. 8.4 shows the MSI dipole source solutions obtained for the grand averaged spike using the sphere and BEM volume conductors. Compared with the true intracranial spike source maximum (Fig. 8.3) the source localization was reasonable in the $x$ and $z$ planes, but shifted posteriorly by more than 2 cm with both the sphere and BEM forward models. Neither data preprocessing with PCA/ICA plus or minus dipole source regularization nor source imaging performed on the combined MEG and EEG data improved upon the validity of the final MSI source localization (Supplementary Fig. 8.S2).

Fig. 8.5 shows the distributed source modeling solution obtained through application of sLORETA to the same MEG data, using a cortical subspace constraint with rotating sources (a solution subspace comprising fixed normal sources in a 20 mm extended cortical patch returned a less valid source maximum, displaced further medially, not shown). The focal maximum within the distributed solution was localized near to the dipole source solution, but the distributed solution extended further medially away from the true intracranial spike source.

Fig. 8.6 shows the dipole source solutions for the 64 individual right anterior temporal spikes analyzed using the sphere volume conductor. Only source solutions with goodness-of-fit $> 80\%$ (expressed as % explained variance, $V$) are shown. Despite the near-identical topographic magnetic flux fields for each spike, source solutions were scattered throughout the right temporal region, including occasional dipole sources situated outside the right temporal lobe. The proportion of dipole source solutions with $V > 80\%$ increased significantly with higher LFF settings, from 25/64 with LFF = 1 Hz to 39/64 with LFF = 3 Hz ($p = 0.021$) to 42/64 with LFF = 6 Hz ($p < 0.005$). With the 1 Hz LFF only 12 of the total 64 dipole sources were valid (as defined in Methods). Most dipole sources with $V \leq 80\%$ were invalid, occasionally localized as far away as the contralateral hemisphere or posterior to the sagittal midpoint. Compared to the 1 Hz LFF, the reliability of dipole source solutions was qualitatively improved and the proportion of valid
solutions increased with the 3 Hz LFF (20/64, \( p = 0.059 \)), though not with the 6 Hz LFF (13/64, \( p > 0.2 \)).

Supplementary Fig. 8.S3 shows the scattered dipole source solutions for the same 64 individual right anterior temporal spikes analyzed using the BEM volume conductor (excluding dipole sources with \( V \leq 80\% \)). The orientations of source solutions obtained with the BEM forward model were far less reliable compared to those obtained with the sphere forward model (Fig. 8.6). The proportion of valid dipole source localizations (as defined in Methods) did not differ significantly between the three different LFF settings using the BEM volume conductor, although large mislocalizations were decreased with the higher LFF settings (e.g., dipole sources mislocalized in the \( x \) plane to the contralateral hemisphere: 10/64 with LFF = 1 Hz, 8/64 with LFF = 3 Hz, 6/64 with LFF = 6 Hz).

8.3.1. Goodness-of-fit and SNR

For individual spikes, dipole source \( V \) and SNR were positively correlated (linear regression: \( R^2 = 0.203; p < 0.001 \), BEM forward model, 1 Hz LFF). Mean values of \( V \) and SNR for individual spike dipole sources were significantly greater with LFF settings of 3 Hz and 6 Hz (\( t \)-test: \( p = 0.012 \) and \( p < 0.0001 \), respectively) than with a LFF setting of 1 Hz (Table 8.1, top row). However, the goodness-of-fit of an individual dipole source solution was not a strong predictor of valid dipole source localization and orientation for individual spikes, even with the higher LFF settings. Using the best combination of sphere forward model and 3 Hz LFF, the proportion of valid individual spike dipole sources was significantly higher among dipole solutions with \( V > 90\% \) (14/25) than among dipole solutions with \( V < 90\% \) (6/39; \( p < 0.001 \)), however, more than two fifths of dipole source solutions with \( V > 90\% \) were not valid (Fig. 8.7). Requirement for an even higher goodness-of-fit, e.g., \( V > 95\% \), excluded most dipole source solutions. With LFF = 1 Hz, no dipole sources met a criterion of \( V > 95\% \); source solutions with
$V > 90\text{-}95\%$ showed qualitatively less source scatter and more reliable source orientation compared to source solutions with $V > 80\text{-}90\%$ (Fig. 8.7 and Fig. 8.8).

SNR was not a reliable predictor of valid dipole source localization for individual spikes, although the worst mislocalizations (e.g., incorrect hemisphere) tended to have lower SNRs (e.g., below 2). Supplementary Fig. 8.S4 demonstrates representative relations between SNRs and dipole source localizations in the $x$ and $y$ planes for individual right anterior temporal spikes.

8.3.2. Spike averaging

Averaging of spikes was associated with significant improvements in the validity of source localization results. Averaging of 2 or more spikes improved SNR, $V$, reliability of source solutions and the proportion of valid solutions at all three tested LFF settings (see Table 8.1, Fig. 8.9 and Supplementary Fig. 8.S5). CEs surrounding source solutions progressively decreased in size with increasing number of spikes averaged with both forward models (see Supplementary Table 8.S1).

Comparing the effects of the 3 Hz and 6 Hz LFF settings on the results obtained for averaged spikes showed both to be associated with increased mean SNR and $V$ values as compared to the 1 Hz LFF setting, most evident with the 6 Hz LFF (Table 8.1). Mean amplitudes of dipole sources were similar with the 1 Hz and 3 Hz LFF settings, but were consistently lower with the 6 Hz LFF (Table 8.1).

Using the sphere volume conductor and LFF = 1 Hz the proportion of valid dipole source solutions was significantly increased after averaging 2 or 4 spikes (both $p < 0.05$) and especially after averaging 8 spikes ($p = 0.0002$), as compared with the analyses performed on individual spikes. With LFF = 3 Hz, there was a significantly greater proportion of valid solutions after averaging 8 spikes ($p = 0.016$; Supplementary Fig. 8.S6). The validity of solutions obtained after spike averaging did not differ significantly between LFF settings.
Fig. 8.10 shows the dipole source solutions obtained after averaging 8 spikes, using the sphere and BEM volume conductors and the three different LFF settings.

Fig. 8.11 shows the MEG waveforms, topographic magnetic flux maps and dipole source solutions for an individual spike and averages of 2, 4, 8, 16, 32 and 64 spikes, demonstrating the progressive decrease in CE volume and stability of source localization and orientation after averaging 8 spikes. The topographic flux fields are similar from the individual spike up to the grand average of all spikes. However, there is a notable decrease in amplitude of the MEG background activity with progressively greater numbers of spikes averaged; the resulting increases in SNR are presumably responsible for the progressive improvements in source localization parameters with spike averaging.

8.3.3. MSI of right mesiobasal temporal lobe spikes

Source localization results similar to those described for the right anterior temporal lobe spikes – with respect to the reliability of dipole source modeling performed on single spikes and the improvements seen with spike averaging – were found with the analysis performed on the 32 presumptive right mesiobasal temporal spikes, and these results are depicted in Fig. 8.12. Using the sphere volume conductor and LFF = 3 Hz, 18/32 scattered dipole source solutions had $V > 80\%$, whereas averages of 8 spikes were consistently associated with $V > 80\%$ and more reliable dipole source localizations and orientations. The dipole source localization obtained for the grand averaged spike appeared physiologically valid, near the intracranially defined spike maximum.

8.4. Discussion

The anterolateral temporal neocortical spike focus that was examined in detail in this study is not ideally situated for MEG analysis because of its significant radial field component (Ahlfors et al., 2010a,b; Huiskamp et al., 2010). Despite this limitation, the anterior temporal focus was selected for this assessment of source modeling reliability because of (a) the large
number of spikes available for study (necessary for the reliability analysis), (b) the classical nature and ubiquity of the anterior temporal spike focus (which – notwithstanding intuitive and published evidence of its disadvantageous orientation for MEG – continues to be used as a subject of investigation for MEG source localization analyses in epilepsy (Baumgartner et al., 2000; Iwasaki et al., 2002; Pataraiia et al., 2005; Kaiboriboon et al., 2010)), and (c) the high amplitude of spikes generated from this focus, which render them easy to visually identify and accurately classify with regard to their morphology and topography.

The results presented in this study confirm previous observations that MSI performed on classical anterior temporal lobe spikes is associated with a consistent tendency toward posterior displacement of the MSI solution within the temporal lobe (Ebersole and Ebersole, 2010). Dipole mapping and distributed source modeling solution maxima were both mislocalized posteriorly to a similar extent.

The reason(s) for this posterior displacement are not completely known but the most parsimonious explanation would be the effect on localization accuracy of the known insensitivity of MEG to radial currents (Ahlfors et al., 2010a,b; Ebersole and Ebersole, 2010; Huiskamp et al., 2010). This, combined with signal cancellation across adjacent sulci in a classical anterior temporal spike source (known to have a cortical extent of approximately 10-20 square centimeters; Tao et al., 2007) will leave gyral crown cortices within the spike focus as the greatest source of non-cancelled electromagnetic activity nearest the location of maximal spike amplitude as determined by intracranial EEG (Ahlfors et al., 2010a; Ebersole and Ebersole, 2010). The anterolateral aspect of the superficial temporal lobe responsible for generation of classical anterior temporal spikes presumably presents a predominantly radial current, which in its anterior most extent is not “seen” by MEG, leaving only the more posterior and basal extent of the cortical generating surface “visible” to MEG, resulting in the posterior displacement of the MSI solution. This interpretation is reinforced by the observations that (a) ESI performed on the simultaneously acquired 19 channel EEG data was able to provide accurate source localization within a
of the intracranially confirmed source location (when performed on the grand average of spikes), despite the relatively few EEG channels, and (b) MSI performed on the grand average of 32 mesiobasal temporal spikes from a focus that presumably presents a predominantly tangential current was also able to provide accurate source localization, despite the relatively low amplitude of the extracranial spike field. The anterior temporal localization results are thus clearly specific to the selected focal anterior temporal lobe spikes studied, whose location and orientation are not optimal for MEG (Huiskamp et al., 2010). However, the main goal of this study was not to examine the physiologic validity of source solutions but rather the reliability, from one spike to the next, of the source modeling methodology. In the future, more detailed examinations of the cancellation effects affecting MEG spikes of varying amplitude and spatial extent will be important to catalogue in a systematic fashion for other brain regions, and to further analyze through numerical simulations (Ahlfors et al., 2010a,b; Huiskamp et al., 2010).

Notwithstanding the inability of MSI to provide a physiologically valid source localization of the anterior temporal spike focus, the reliability of the MSI methodology was testable in this study by looking for reproducibility of source localization results from one spike to the next, given that the true cortical source of each individual spike was known in this patient to be essentially identical (from intracranial recordings). In this regard, the observed scatter of source solutions obtained when modeling these identical spikes demonstrated that the clustering of MSI dipole sources was due to limitations in reliability of the technique. It is possible that this finding may be relevant to the physiologic interpretation of most, if not all, clusters of scattered MSI dipole sources in patients with focal epilepsy. Qualitative analysis of dipole sources associated with this patient’s mesiobasal temporal spike focus showed the same limitations in reliability when modeling single spikes. It is also relevant to the evaluation of reliability of other spike source imaging methods that involve averaging multiple spike source images, or that attempt to model the spatial extent of single spike source activity (Shiraishi et al., 2011; Uda et al., 2012; de Gooijer-van de Groep et al., 2013; Mohamed et al., 2013).
High goodness-of-fit values were definitely associated with decreased scatter (i.e. improved reliability) as well as improved source localization validity (at the lobar level) when modeling individual spikes, although even source solutions with $V > 90\%$ were scattered quite widely throughout the temporal lobe (and a requirement for even higher goodness-of-fit, e.g., $V > 95\%$, would have excluded most spikes from the analysis). The proportion of spikes meeting reasonable goodness-of-fit values was increased and the reliability of source solutions improved when modeling single spikes with the use of a higher LFF setting (e.g., 3 Hz). Reducing the power of low frequency background activity fluctuations and thereby increasing SNR is presumably responsible for the slight improvement in reliability seen with a higher LFF when modeling individual spikes.

Unexpectedly, the single sphere forward model (volume conductor) was associated with better reliability for MSI, particularly in terms of dipole source orientation, than the realistic head shaped BEM volume conductor. The reasons for this are unknown, particularly when a realistic head shaped BEM volume conductor was associated with very accurate dipole source localization and orientation attained when modeling the simultaneous 19 channel EEG data for the same spikes. We can only speculate that the use of only a single conducting layer in the MEG BEM forward model resulted in an incorrect or biased correction for volume currents that degraded the overall solution, such that no correction provided better results.

Signal averaging performed on increasing numbers of spikes significantly improved the reliability of source solutions and, once more than 8 spikes were averaged, removed any benefits of the higher LFF settings. The advantages of spike averaging presumably arise from the associated increase in SNR (Stephen et al., 2003; Van’t Ent et al., 2003; Bast et al., 2004, 2006), and most specifically from diminishing the power of the background MEG signal (i.e., noise), rendering the averaged spontaneous spike potential more analogous to an evoked potential.

8.4.1. Recommendations
The findings in this particular study are of course limited specifically to spikes generated from the anterolateral temporal neocortex, an area confirmed here to contain brain regions for which MEG may lack sufficient sensitivity. Nonetheless, the observations on reliability likely have broader applicability and the demonstration that dipole source scatter may often be related to the limitations in reliability of the source localization techniques, rather than the extent of the underlying epileptogenic cortex, is an important finding with regard to the physiological interpretation of clusters of dipole sources.

If it is necessary to perform MSI on single spikes, it would appear that a LFF of 3 Hz or even 6 Hz is preferable to a more standard 1 Hz setting. It would also appear that a single sphere forward model may be sufficient for MSI.

As with ESI, spike averaging appears to be of paramount importance with regard to improving the reliability of the noninvasive source localization methodology. An optimal number of spikes to average cannot be determined with certainty from this investigation, although averaging a minimum of 8 spikes would seem to be advisable and benefits continued to be seen with averages of 16, 32 and even 64 spikes with respect to decreased CE volume and improved SNR and goodness-of-fit values. It is of course imperative that only spikes arising from a well defined single spike focus are included in the averaging process, something which still requires careful analysis of the topographic spike fields by a clinical neurophysiologist prior to spike averaging. Further research into methods that may accurately classify subpopulations of topographically identical spikes in an automated fashion will be important in the continued development of MSI in epilepsy (Van’t Ent et al., 2003; Mohamed et al., 2013).
Table 8.1. SNR and $V$ of right anterior temporal MEG spikes; individual (n=64) and averaged ($2^x$, x=1,2,3...6) spikes, different LFFs (1 Hz, 3 Hz, 6 Hz).

<table>
<thead>
<tr>
<th></th>
<th>MEG</th>
<th>LFF 1 Hz</th>
<th>LFF 3 Hz</th>
<th>LFF 6 Hz</th>
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<td></td>
<td>Amp. (µAmm)</td>
<td>SNR</td>
<td>V (%)</td>
<td>Amp. (µAmm)</td>
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<tr>
<td>Ind. Spikes</td>
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<tr>
<td>(n=64)</td>
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<td></td>
<td>1468.5 ± 1476</td>
<td>1.75 ± 0.6</td>
<td>75.5 ± 16.2</td>
<td>1651.8 ± 1330</td>
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<td>Av. 2 spikes</td>
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<tr>
<td>(n=32)</td>
<td>1142.0 ± 910</td>
<td>2.08 ± 0.8</td>
<td>80.7 ± 17.0</td>
<td>1213.7 ± 920</td>
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<tr>
<td>Av. 4 spikes</td>
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<tr>
<td>(n=16)</td>
<td>1230.3 ± 809</td>
<td>2.56 ± 0.5</td>
<td>84.7 ± 19.0</td>
<td>1240.6 ± 696</td>
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<tr>
<td>Av. 8 spikes</td>
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<td>(n=8)</td>
<td>919.4 ± 663</td>
<td>3.83 ± 0.8</td>
<td>93.2 ± 3.6</td>
<td>908.4 ± 753</td>
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<tr>
<td>Av. 16 spikes</td>
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<tr>
<td>(n=4)</td>
<td>507.5 ± 616</td>
<td>4.9 ± 0.7</td>
<td>95.3 ± 1.7</td>
<td>1204.6 ± 1174</td>
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<td>Av. 32 spikes</td>
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<td>(n=2)</td>
<td>1192.2 ± 1022</td>
<td>6 ± 0.1</td>
<td>93.1 ± 3.5</td>
<td>613.7 ± 583</td>
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<tr>
<td>Av. 64 spikes</td>
<td></td>
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<td>(n=1)</td>
<td>921.5 ± 838</td>
<td>8.3 ± 0.3</td>
<td>95.7 ± 5.5</td>
<td>240.2 ± 8.7</td>
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Amp.=amplitude, Av.=average, Ind.=individual, LFF=low frequency filter, SNR=signal to noise ratio, $V$=variance

**=p<0.01 (compared with LFF 1 Hz value); *=p<0.05 (compared with LFF 1 Hz value)
Fig. 8.1. Examples of 8 spikes generated within the anterolateral temporal neocortical spike focus identified with stereoelectroencephalographic (simultaneous scalp and intracranial subdural and depth electrode) recordings obtained during presurgical clinical investigations (see Wennberg et al., 2011). The intracranial spike fields (left) show a consistent amplitude maximum at subdural electrode contact RTA2. The simultaneously acquired scalp EEG shows that the neocortical spikes are associated with an anterior temporal extracranial spike field maximal at F8 (right). Sensitivity 70 μV/mm for intracranial EEG, 10 μV/mm for scalp EEG; common average reference montage for both scalp and intracranial EEG, the average reference comprising 12 scalp electrodes (F3, F4, C3, C4, P3, P4, O1, O2, T3, T4, T5, T6); LFF 0.5 Hz, HFF 70 Hz.
Figure 8.2

**Fig. 8.2.** Averaged (n = 64) right anterior temporal lobe spike waveforms recorded during simultaneous MEG and EEG investigation. MEG waveform (green), EEG waveform (blue). MSI (*top*) and ESI (*bottom*) dipole source solutions (*left*), shown on high resolution cortical reconstruction of patient’s own brain MRI. MEG (*top*) and EEG (*bottom*) topographic waveform plots and electromagnetic field maps (*right*). Spikes averaged on EEG contact with maximal peak amplitude (F8; n = 64). MGFP = mean global field power; LFF 1 Hz, HFF 30 Hz; common average reference for 19 channel scalp EEG.
Fig. 8.3. Localization of right anterior temporal spike maximum on patient’s pre-operative high resolution MRI as determined from intracranial subdural and depth electrode recordings (left; green crosshairs mark the location of subdural electrode contact RTA2 in Fig. 1; \( x = 47.5 \) mm, \( y = 34.6 \) mm, \( z = 18.9 \) mm). ESI dipole source solutions (and surrounding CEs) obtained for averaged (\( n = 64 \)) right anterior temporal EEG spikes recorded using 19 electrodes of standard 10-20 system during stereoelectroencephalography investigation (middle) and MEG/EEG investigation (right). Same stereoelectroencephalography data set as in Fig. 7.4 in (Wennberg and Cheyne, 2013), except subtemporal and zygomatic electrodes excluded from dipole source calculations. CEs were larger and source localization was shifted rightward, forward and especially upward in the absence of subtemporal electrodes (compare with Fig. 7.4 in (Wennberg and Cheyne, 2013)). Nevertheless, even with only 19 electrodes, similar physiologically valid dipole source localizations were obtained using scalp EEG data acquired in both the stereoelectroencephalographic (\( x = 50.5 \) mm, \( y = 41.0 \) mm, \( z = 28.5 \) mm) and MEG/EEG (\( x = 44.5 \) mm, \( y = 36.3 \) mm, \( z = 22.0 \) mm) studies. Volume conductor = BEM; LFF = 1 Hz.
Fig. 8.4. Dipole source solutions (and surrounding CEs) obtained for averaged (n = 64) right anterior temporal MEG spikes from MEG/EEG investigation using (left) a single sphere volume conductor (sources depicted on MNI averaged brain MRI) and (right) the BEM volume conductor created from the patient’s own MRI (sources depicted on patient’s own MRI). LFF = 1 Hz. Although localization coordinates were reasonable in the x and z planes, MEG dipole sources were shifted posteriorly by more than 2 cm with both the sphere (x = 48.5 mm, y = 11.5 mm, z = 22.2 mm) and BEM (x = 51.0 mm, y = 9.5 mm, z = 27.5 mm) forward models.
Figure 8.5

**Fig. 8.5.** Distributed source modeling of averaged (n = 64) right anterior temporal MEG spikes using sLORETA. Same EEG data used for dipole mapping in Fig. 8.4. LFF = 1 Hz. Volume conductor = sphere; cortical solution subspace constraint with rotating sources, no extension; cutoff threshold for display set at 75% (solutions with smaller explained field percentages (as a percentage of the largest current) are excluded from display). LFF = 1 Hz. The distributed source solution had a localized maximum value at $x = 42.4$ mm, $y = 11.7$ mm, $z = 24.6$ mm ($V = 98.72\%$), near (6.1 mm medial to) the dipole source solution shown at bottom right. The distributed source solution extended further medially away from the true anterolateral temporal neocortical spike generator.
Fig. 8.6. Dipole source solutions for individual right anterior temporal MEG spikes; sphere volume conductor. Dipole sources with $V \leq 80\%$ excluded. Columns, from left to right, show solutions for spike groups 1-16, 17-32, 33-48 and 49-64. (A) LFF = 1 Hz. (B) LFF = 3 Hz. (C) LFF = 6 Hz. LFF settings of 3 Hz and 6 Hz increased the number of dipole sources meeting goodness-of-fit criterion ($V > 80\%$). Scattered source solutions mostly clustered within right temporal lobe, however, reliability and intralobar validity were not particularly good with any of the LFF settings. Sources depicted on MNI averaged brain MRI.
Figure 8.7

**Fig. 8.7.** Goodness-of-fit as a predictor of “valid” dipole source localization and orientation for individual MEG spikes. Localization was deemed valid (correct) for dipole sources situated within 1 cm on either side, in the x, y and z planes, of the grand average MEG source solution (x = 48.5 mm, y = 11.5 mm, z = 22.2 mm), accepting a consistent posterior displacement of MEG sources away from the true intracranial cortical source. Dipole vectors that projected anteriorly or anterolaterally through temporal neocortex were deemed valid (correct). Volume conductor = sphere. With LFF = 1 Hz, 54.5% of dipole sources with $V > 90\%$ were valid, compared with 12.8% of dipole sources with $V \leq 90\%$ (left); with LFF = 3 Hz, 56% of dipole sources with $V > 90\%$ were valid, compared with 15.4% of dipole sources with $V \leq 90\%$ (right). Most dipole sources with $V \leq 80\%$ were invalid.
Fig. 8.8. Goodness-of-fit and dipole source solutions for individual right anterior temporal MEG spikes (with $V > 80\%$); sphere volume conductor, sources plotted on patient’s own brain MRI. Solutions with lower $V$ (top) associated qualitatively with increased source scatter and less reliable dipole orientation compared to solutions with higher $V$ (bottom). LFF = 1 Hz. Dipole source goodness-of-fit levels indicated in color; yellow $V > 90-95\%$, cyan $V > 85-90\%$, green $V > 80-85\%$. 
Fig. 8.9. Bubble plot showing three dimensional dipole source localization for each of the 64 right anterior temporal MEG spikes. Dipole source localizations for averages of 8 spikes (spikes 1-8, 9-16...57-64) shown superimposed in bold. Volume conductor = BEM. LFF = 3 Hz. Abscissa: x plane (left/right). Ordinate: y plane (anterior/posterior). Bubble size represents location in z plane (superior/inferior, larger bubble more superior).
Figure 8.10

Fig. 8.10. Dipole source solutions for averages of 8 right anterior temporal MEG spikes (spikes 1-8, 9-16...57-64) with LFF = 1 Hz (left), LFF = 3 Hz (middle) and LFF = 6 Hz (right). (A) Volume conductor = sphere. (B) Volume conductor = BEM. Reliability and validity of source solutions were not improved with higher LFF settings. Orientation of dipole sources less reliable with the BEM forward model at all three LFF settings.
Fig. 8.11. MEG waveforms, topographic magnetic flux maps and dipole source solutions (and surrounding CEs) for individual spike 1, the average of spikes 1 and 2, the average of spikes 1-4, the average of spikes 1-8, the average of spikes 1-16, the average of spikes 1-32, and the average of spikes 1-64. Volume conductor = sphere; LFF = 1 Hz. Dipole sources depicted overlying a high-resolution cortex segmentation of the MNI averaged MRI dataset. Despite minimal
differences in the measured topographic flux fields, dipole source solutions differed widely between the individual spike and the averages of the first two or four spikes. Averaging of the first 8, 16, and 32 spikes produced stable dipole source solutions and progressively smaller CEs (further reduced with the grand average of 64 spikes).
Figure 8.12
Fig. 8.12. (A) Averaged spikes (n = 203) generated within the mesiobasal temporal neocortical spike focus identified with stereoelectroencephalographic (simultaneous scalp and intracranial subdural and depth electrode) recordings obtained during presurgical clinical investigations. The intracranial spike field (left) shows maximal negative spike amplitude at the medial contacts of the basal temporal subdural electrode (RTB1-3). The simultaneously acquired scalp EEG shows that the mesiobasal focus is associated with a very low amplitude lateral temporal extracranial spike field at T4, T6 (right). Sensitivity, filters, montage as in Fig. 8.1. (Adapted from Fig. 6 in Wennberg et al., 2011). (B) Averaged MEG waveform (n = 32) and associated MEG and simultaneous 19 channel EEG topographic maps for the mesiobasal spike focus. Spike amplitude much lower for this focus than for the anterior temporal focus: MEG sensitivity scale bar = 200 fT (compared to 1000 fT in Fig. 2, i.e., gain of MEG signal increased five-fold for depiction of this mesiobasal spike field). (C) Scattered dipole source solutions for individual right mesiobasal spikes with $V > 80\%$ (n = 18). Dipole source goodness-of-fit levels indicated in color; yellow $V > 90-95\%$, cyan $V > 85-90\%$, green $V > 80-85\%$ (left). Reliability was qualitatively improved (i.e., scatter decreased and dipole orientations more consistent) with MSI performed on averages of 8 spikes (spikes 1-8, 9-16, 17-24, 25-32, 5-12, 13-20 and 21-28). Dipole source goodness-of-fit levels indicated in color; orange $V > 95\%$, yellow $V > 90-95\%$, cyan $V > 85-90\%$, green $V > 80-85\%$ (insets). Dipole source solution (and surrounding CE) for the grand average of 32 spikes localized accurately near the mesiobasal temporal neocortical region of maximal intracranial spike amplitude (right). Volume conductor = sphere; LFF = 3 Hz.
Supplementary data to: Reliability of MEG source imaging of anterior temporal spikes: analysis of an intracranially characterized spike focus

Supplementary Table 8.S1. CEs of right anterior temporal MEG spikes; individual (n=64) and averaged \((2^x, x=1,2,3...6)\) spikes, BEM and Sphere volume conductors, different LFFs (1 Hz, 3 Hz, 6 Hz).

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<th>LFF 1 Hz</th>
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<th>LFF 6 Hz</th>
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<tr>
<td></td>
<td>BEM</td>
<td>Sphere</td>
<td>BEM</td>
<td>Sphere</td>
<td>BEM</td>
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<tr>
<td>Ind. Spikes</td>
<td>174.1±350</td>
<td>383.7±656</td>
<td>126.5±526</td>
<td>222.1±456</td>
<td>61.07±165</td>
<td>357.8±1624</td>
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<td>(n=64)</td>
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<tr>
<td>Av. 2 spikes</td>
<td>59.76±134</td>
<td>151.8±173</td>
<td>29.78±68.4</td>
<td>130.5±204</td>
<td>31.79±93.4</td>
<td>71.48±87.6</td>
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<td>Av. 4 spikes</td>
<td>1.68±3.5</td>
<td>125.9±240</td>
<td>3±7.6</td>
<td>52.12±65.3</td>
<td>1.64±2.7</td>
<td>24.18±23.6</td>
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<td>(n=16)</td>
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<td>Av. 8 spikes</td>
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<td>7.84±3.7</td>
<td>0.61±0.6</td>
<td>5.98±2.9</td>
<td>0.56±1.2</td>
<td>5.56±3.9</td>
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<td>Av. 16 spikes</td>
<td>2.2±2.4</td>
<td>3.05±0.6</td>
<td>1.28±1.5</td>
<td>3.98±4.0</td>
<td>0.65±0.8</td>
<td>1.48±0.3</td>
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<tr>
<td>Av. 32 spikes</td>
<td>0.05±0.1</td>
<td>1.35±0.4</td>
<td>0.35±0.5</td>
<td>3.95±3.9</td>
<td>0.05±0.1</td>
<td>0.75±0.4</td>
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<tr>
<td>Av. 64 spikes</td>
<td>0</td>
<td>0.5</td>
<td>0.2</td>
<td>0.4</td>
<td>0</td>
<td>0.2</td>
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<td>(n=1)</td>
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Av.=average, BEM=boundary element method, Ind.=individual, LFF=low frequency filter
Supplementary Figure 8.S1

**Mean percentage of maximum peak-peak amplitude at right temporal intracranial electrode sites (n=142 spikes)**

![Bar chart showing mean percentage of maximum peak-peak amplitude at different right temporal lobe intracranial electrode contacts.](image)

**Fig. 8.S1.** Mean right anterior temporal spike amplitude ratios (and standard deviations) at the different right temporal lobe intracranial electrode contacts (as a percentage of the maximum peak to peak amplitude at RTA2). Measurements made on the 142 right anterolateral temporal neocortical spikes presented in (Wennberg et al., 2011). RTD = right temporal depth electrode, implanted orthogonally through middle temporal gyrus, aimed at anterior hippocampus; contact 1 most medial, contact 4 most lateral (**Fig. 8.1**). RTA = right anterior temporal subdural strip electrode; contact 1 most anterior/medial, contact 4 most posterior/lateral (**Fig. 8.1**). RTB = right temporal basal subdural strip electrode; contact 1 most medial, contact 4 most lateral (**Fig. 8.1**). RTP = right posterior temporal subdural strip electrode, implanted along middle temporal gyrus posterior to RTA (Wennberg et al., 2011); contact 1 most posterior, contact 4 most anterior (overlying midtemporal lateral neocortex). Center to center intercontact distances = 1 cm.
Fig. 8.S2. Effects of data preprocessing with PCA/ICA (two principal components with SNR > 1.0; three independent components), dipole component regularization ($\lambda = 1.0$) and inclusion of simultaneous EEG data (conductivity factor = 1.94) on source localization solutions of averaged (n = 64) right anterior temporal MEG spikes. LFF = 1 Hz. Neither PCA/ICA filtering (with or without regularization) nor inclusion of EEG data resolved the posterior shift of the MEG dipole source solution.
Supplementary Figure 8.S3
Fig. 8.S3. Dipole source solutions for individual right anterior temporal MEG spikes; BEM volume conductor. Dipole sources with $V \leq 80\%$ excluded. Columns, from left to right, show solutions for spike groups 1-16, 17-32, 33-48 and 49-64. (A) LFF = 1 Hz. (B) LFF = 3 Hz. (C) LFF = 6 Hz. Use of the individualized BEM volume conductor led to solutions that were qualitatively more scattered (i.e., less reliable) than those obtained with the sphere forward model at all LFF settings (compare with Fig. 8.6). Dipole source orientations were markedly less reliable with the BEM forward model (compare with Fig. 8.6), despite the similarity of MEG/EEG topographic fields for all 64 spikes. The scatter of MEG dipole sources was only questionably decreased at the higher LFF settings. Sources depicted on patient’s own brain MRI.
Supplementary Figure 8.S4

**Fig. 8.S4.** SNR as a predictor of valid dipole source localization for individual right anterior temporal MEG spikes. LFF = 1 Hz. Volume conductor = BEM. SNR was not a strong predictor of dipole source proximity to true intracranial source in $x$ plane (dotted vertical line, 47.5 mm, top), although all sources falsely localized to the wrong side of the head had SNR values below 2. The posterior shift of MEG dipole sources away from the true intracranial localization in the $y$ plane (dotted vertical line, 34.6 mm, bottom) is evident; SNR for individual spikes was not a good predictor of dipole source proximity to the localization of the averaged ($n = 64$) MEG spike in the $y$ plane (located at $y = 9.5$ mm with the BEM forward model), although almost all of the sources localized more than 2 cm away from the averaged spike localization had SNR values below 2.5.
Supplementary Figure 8.S5

MEG dipole source localizations, x, y, and z planes, BEM

- LFF 1 Hz
- LFF 3 Hz
- LFF 6 Hz
Fig. 8.S5. Effects of spike averaging and LFF setting on MEG dipole source localizations in x (red diamonds), y (blue triangles) and z (grey circles) planes. Horizontal dotted lines indicate true intracranial source localization in x (red, 47.5 mm), y (blue, 34.6 mm) and z (grey, 18.9 mm) planes. Volume conductor = BEM. LFF settings of 3 Hz and 6 Hz slightly reduced scatter (improved reliability) of individual and averaged spike dipole sources compared with LFF = 1 Hz. (Falsely localized extreme outlier data points beyond the range of ordinate axis not shown: for LFF = 1 Hz, n = 7 Ind. spikes, n = 4 Ave. 2, n = 1 Ave. 4; for LFF = 3 Hz, n = 9 Ind. spikes, n = 3 Ave. 2; for LFF = 6 Hz, n = 6 Ind. spikes, n = 2 Ave. 2.) Spike averaging improved reliability and validity (in x and, to a lesser extent, z planes) of source solutions at all LFF settings. Dipole source localizations and orientations for the grand average of 64 MEG spikes varied with the different LFF settings. Ind. = individual, Ave. 2 = average of 2 spikes (1-2,3-4...63-64), Ave. 4 = average of 4 spikes (1-4,5-8...61-64), Ave. 8 = average of 8 spikes (1-8,9-16...57-64), Ave. 16 = average of 16 spikes (1-16, 17-32...49-64), Ave. 32 = average of 32 spikes (1-32,33-64), Ave. 64 = average of all 64 spikes.
Supplementary Figure 8.S6

Fig. 8.S6. Effects of spike averaging on dipole source localization and orientation for right anterior temporal MEG spikes, sphere volume conductor, LFF = 1 Hz (left) and LFF = 3 Hz (right). Localization was deemed "valid" (correct) for dipole sources situated within 1 cm on either side, in the x, y and z planes, of the grand average MEG source solution (x = 48.5 mm, y = 11.5 mm, z = 22.2 mm), accepting a consistent posterior displacement of MEG sources away from the true intracranial cortical source. Dipole vectors that projected anteriorly or anterolaterally through temporal neocortex were deemed valid. LFF setting of 3 Hz associated with a trend toward a greater number of valid dipole sources for individual spikes. With LFF = 1 Hz, validity of source solutions was improved after averaging 2 (p = 0.039), 4 (p = 0.037), 8 (p < 0.001) or more spikes. With LFF = 3 Hz, validity of source solutions was improved after averaging 8 (p = 0.016) spikes.
Chapter Nine

General Discussion
GENERAL DISCUSSION

K-complex results

The first study (Chapter 4) led to the delineation of the intracranial cortical localization of the brain regions responsible for generation of the human K-complex (Wennberg, 2010b). The intracranial K-complex field appears maximal and surface negative over the anterior and superior aspects of the medial and lateral frontal lobe cortices, consistent with the frontal midline scalp negative EEG maximum. Polarity inversion is seen in the white matter of the frontal lobe, the subcortical polarity inversion consistent with the classical dipole layer model presumed to underlie generation of most (and certainly all large amplitude) potentials in the EEG (Gloor, 1985): electrode contacts within the frontal white matter record the opposite, positive side of the surrounding surface-negative frontal dipole layer. Farther away, the large, anteriorly and superiorly maximal surface negative field is volume conducted posteriorly and inferiorly in the brain as an inverted, positive field, the polarity reversing laterally above the inferior temporal region and medially above the cingulate cortex.

This intracranial field indicates that K-complexes are generated by widespread synchronous cortical activity arising maximally within the superior medial and lateral frontal cortices, removing any doubt that these waveforms might be focally generated in deep cortical midline structures or even the thalamus, improbable historical concepts that have been sometimes erroneously supported by noninvasive source localization studies (Colrain, 2005). In line with the dipole layer model, the surface negative peak of the K-complex must represent the effects of either: (a) summated excitatory post-synaptic potential (EPSP) inputs to the superficial apical dendrites of frontal lobe cortical pyramidal cells, or (b) summated inhibitory post-synaptic potential (IPSP) inputs at the deeper cell soma level of these same pyramidal cells. The bulk of the available evidence obtained from animal and human microelectrode recordings supports the second option: i.e., that synchronized hyperpolarizing IPSPs synapsing on pyramidal cell bodies
in deeper layers of the cortical mantle are primarily responsible for initiation of the principal negative wave of the K-complex (Cash et al., 2009; Cserea et al., 2010; Dalal et al., 2010; Le Van Quyen et al., 2010).

The localization of the presumptive inhibitory inputs is unknown; however, it is reasonable to implicate the thalamus (and possibly other subcortical structures) given the known involvement of reciprocal thalamocortical circuits in slow oscillatory sleep patterns (Amzica and Steriade, 1998, 2002; Steriade and Amzica, 1998).

The results of the first study (Wennberg, 2010b) contributed new, useful information to the field of sleep neurophysiology. For the purposes of this thesis, however, identification of the intracranial cortical localization of the K-complex served as a tool with which one could assess the reliability and validity of noninvasive electromagnetic source imaging applied to large, bilaterally synchronous cortical sources. Findings obtained through analyses performed on the K-complex were considered likely to have relevance also to the slow waves of deep non-REM sleep as well as the classical generalized 3 Hz spike and wave discharges of primary generalized epilepsy. Not only are the surface negative voltage topographic peaks of the spike, wave, and K-complex components highly similar, but K-complexes and spike and wave discharges in patients with primary generalized epilepsy are frequently intermingled, and likely share similar thalamocortical network circuitry, anatomically and physiologically (Gloor, 1968; Snead III, 1995; Amzica and Steriade, 2002).

In the third study (Chapter 6), it was found that no combination of the tested forward and inverse models could accurately provide a localization result in keeping with the widespread superficial cortical source (Wennberg and Cheyne, 2013). Noninvasive source imaging of K-complexes could be highly reliable but, unfortunately, was not physiologically valid. Source localization solutions returned by different dipole mapping or distributed source modeling algorithms were invariably falsely localized to deep interhemispheric structures. Although we expected that single dipole mapping approaches would be prone to such incorrect solutions,
surprisingly, distributed source modeling, a technique hypothetically more attractive than single
dipole mapping given the known distribution of the electrical generating source across an
extended area of cortex, returned similar deep physiologically invalid solutions as were provided
with dipole mapping. Different choices of more or less realistic solution spaces for distributed
modeling did not improve the validity of localization results.

These findings provide further evidence of the propensity of source localization
algorithms to provide deep interhemispheric solutions for signals generated by large synchronous
cortical sources (Nunez, 1990; Romani and Pizzella, 1990; Hämäläinen et al., 1993; Numminen
et al., 1996; Kobayashi et al., 2005; Zumsteg and Wennberg, 2005), and distributed modeling
appears to offer no advantage over dipole mapping in this regard.

The implications of these results extend beyond the study of K-complexes because
similar deep interhemispheric localization solutions have been reported – and presumed to be
accurate – in modeling studies of other large synchronous sources such as sleep slow waves
(Murphy et al., 2009) and generalized spike and wave complexes in epilepsy (Rodin et al., 1994;
Holmes et al., 2004; Tucket et al., 2007).

As an example of the probable generalizability of our K-complex ESI and MSI results to
the study of generalized spike and wave discharges, Fig. 9.1 shows the results of ESI performed
on (a) the spike of a spike/wave complex, (b) the wave of a spike/wave complex, and (c) the peak
of a K-complex. Essentially identical source localization results were obtained for all three
potentials, using both dipole mapping and distributed source modeling. From our K-complex
results, it is known that the ESI results are not physiologically valid. One has good reason to
assume that the spike and wave results are similarly invalid. Fig. 9.2 shows similar deep midline
MSI source localization results obtained with distributed modeling of the spikes recorded during
a generalized absence seizure.

From these observations, it is suggested that previous studies that have used noninvasive
source localization techniques as a basis to explore the (patho)physiological underpinnings of
high amplitude, bilaterally synchronous electromagnetic potentials, such as K-complexes, sleep slow waves, and spike and wave discharges, must be regarded with circumspection. Further research is needed to determine new, more appropriate modeling approaches for these large electro(magneto)graphic events.

*Anterior temporal spike results*

The second study (Chapter 5) delineated the cortical regions involved in the generation of different temporal lobe spike foci in patients with MTLE (Wennberg et al., 2011). The typical anterior temporal spikes recorded with EEG and MEG in MTLE were generated in the anterolateral temporal neocortex. The absence of coincident spiking at mesial locations indicated that these were neither propagated from nor to the hippocampus. Spikes with an electrical field maximal over the mid temporal region were generated in the lateral temporal neocortex and likewise did not involve the hippocampus. Individual spikes generated in the mesiobasal temporal neocortex, including the fusiform gyrus, were difficult to detect with EEG and only slightly more identifiable with MEG. Spikes generated within and confined to the mesial temporal structures, as confirmed by intracranial recordings, could not be detected with EEG or MEG. Notably, such spikes could not be detected even at intracranial recording sites on the lateral surface of the temporal lobe.

The significance of these findings is that spikes recorded with EEG and MEG in MTLE are localized to neocortical foci, and not to the mesial temporal structures. Accordingly, noninvasive ESI and MSI cannot – in the absence of simultaneous intracranial EEG identification of mesial temporal spikes and subsequent spike averaging – accurately identify mesial temporal spike sources. The results of this study should put to rest any further debate on these issues (Alarcón and Agirre-Arrizubieta, 2011).

The intracranial cortical source localizations of the temporal lobe spike foci, and specifically that of the classical anterolateral temporal neocortical source, served as the gold
standard by which to assess the reliability and validity of electromagnetic source imaging of interictal spikes arising from a typical, lateralized cortical source.

The fourth study (Chapter 7) was a detailed reliability and validity analysis of source solutions obtained when performing ESI on a large collection of identical temporal lobe spikes (Wennberg and Cheyne, 2014b). The results showed that ESI performed on averaged spikes from a classical anterior temporal lobe spike focus was able to depict the true intracranial cortical source maximum with surprisingly high (subcentimeter) accuracy, using only a standard clinical array of 27 EEG electrodes. For this archetypal anterolateral temporal neocortical spike source, ESI of averaged spikes did not provide solutions falsely localized deep to the true superficial cortical source, in contrast to the ESI results obtained for the large, bilateral source of the K-complex, where deep mislocalizations appear to be inevitable solutions of both dipole mapping and distributed source modeling (Wennberg and Cheyne, 2013). The upper size limit of an extended cortical source that may be accurately modeled with existing noninvasive source imaging techniques is unknown, but must lie between the extent of an anterior temporal spike focus and the much larger bifrontal cortical distribution of the K-complex.

The validity of ESI solutions obtained for single spikes was inconsistent, i.e., modeling performed on individual anterior temporal spikes was not highly reliable. Reliability (and the proportion of valid solutions) was better with a LFF setting of 3 Hz (and, to a lesser extent, 6 Hz) as compared to a 1 Hz LFF setting, likely reflecting the greater mean SNR obtained with the higher LFF settings.

In this study (Wennberg and Cheyne, 2014b; Chapter 7), the true cortical source of each spike was known to be identical from the simultaneous intracranial EEG recordings such that any scatter of ESI solutions could be directly attributed to limitations in reliability of the noninvasive source localization methodology. The results on reliability suggest that clusters of scattered dipole sources should not be taken as evidence of the extent of the brain region responsible for generation of the extracranially recorded spikes. Instead, at least as a first hypothesis, scattered
clusters of dipole sources should be taken as a sign suggesting limited reliability of the source imaging method. The evidence presented in this study was concentrated on typical, non-propagated anterior temporal lobe spikes, however, there is no reason to expect that the implications of dipole source scatter might not apply equally to focal spike generators situated in other brain regions. In fact, strong evidence supporting the idea that scattered dipole sources represent limitations in the reliability of ESI performed on single spikes, rather than the extent of an epileptogenic brain region, has been previously published (Bast et al., 2004, 2006).

Spike averaging was the single most effective operator dependent intervention in the source imaging methodology and it was able to improve both the reliability and validity of ESI (Wennberg and Cheyne, 2014b; Chapter 7). SNR, goodness-of-fit, reliability of source solutions and the proportion of valid source solutions progressively increased with averages of greater numbers of spikes, at all three of the LFF settings tested and with both of the tested volume conductors. Statistically significant improvements in the proportion of valid source solutions were noted with averages of 4 spikes, the significance further improving with averages of 8 or more spikes. Indeed, the benefits identified with the higher LFF settings in ESI performed on single spikes (presumably attributable to selective reduction of low frequency background activity components, which are typically of larger amplitude than higher frequency background activity and thus likely to contribute relatively more power to the background noise) became insignificant once 4 or more spikes were averaged. Interestingly, the known benefits of an individualized realistic volume conductor (confirmed in this study in the analysis of single spikes) essentially disappeared when averages of 8 or more identical spikes were used for ESI.

The findings of this study align well with the few previous reports that systematically addressed the issue of spike averaging (Krings et al., 1999; Bast et al., 2006). The benefits of spike averaging presumably result primarily from increasing the SNR of the modeled spike through the progressive diminution of background EEG activity that is realized with increasing
numbers of averaged spikes, rendering the signal more and more analogous to an evoked potential.

A crucial requirement in the averaging process as applied to epilepsy, unlike evoked potential recordings, is that one must ensure that only “identical” spontaneous epileptiform potentials are grouped for averaging. Currently, such a process cannot be automated without compromising the accuracy of determination of identicality of the spike field. At this point, careful analysis of the topographic distribution of individual spontaneous spikes by a trained electroencephalographer is necessary to ensure that only spikes arising from a single focus are included in the averaging process.

Another issue of clinical relevance related to spike averaging is the need to capture a sufficient number of identical spikes. This could prove to be difficult to accomplish in many patients in the outpatient laboratory setting. However, all patients undergoing presurgical investigations will presumably have performed at some point continuous high quality EEG-video recording, and for most patients this already routine stage of investigation should be sufficient to capture enough spikes to enable spike averaging for source imaging purposes.

The accuracy of localization of source maxima was similar between the two inverse models tested, the fixed coherent dipole mapping method and sLORETA, the latter a minimum norm estimation based distributed source modeling algorithm. In general, distributed source modeling of individual spikes with sLORETA did not improve upon the localization of source maxima obtained with dipole mapping.

In that the true cortical source of a spontaneous interictal epileptiform discharge is distributed over an extent of cortex, it is conceptually appealing to think that a distributed source localization algorithm might be able to provide an estimation of the extent of the cortical spike generator. However, for the anterior temporal lobe spike field examined in this study, sLORETA was unable to provide useful information pertaining to the cortical extent of the spike generator. Moreover, the use of arbitrarily selected cutoff thresholds introduces a non-evidence-based
operator bias to the displayed sLORETA results, decreasing objectivity and limiting potential clinical utility for determination of the extent of epileptogenic cortex.

Whether ESI should be performed at the spike peak or mid upswing is a matter of debate (Merlet and Gotman, 1999; Ebersole, 2000; Lantz et al., 2003b; Bast et al., 2006; Ray et al., 2007; Ebersole and Hawes-Ebersole, 2007; Plummer et al., 2010b, Wang et al., 2011). In this study, modeling performed at the mid upswing of the grand averaged spike, although associated with a lower SNR, lower goodness-of-fit and larger CE than that obtained with modeling at the spike peak, provided a physiologically valid source localization (with the BEM volume conductor) that differed little from that obtained with modeling the grand average at the spike peak. However, in the analysis of single spikes, mean SNR and mean $V$ were markedly reduced when modeling was performed at the mid upswing, and the source solutions obtained were less reliable and less likely to be accurately localized.

Recommendations based on this ESI study may not be generalizable to spike foci situated in other brain regions. Nevertheless, the anterolateral temporal neocortical spike generators investigated represent the most common of all spike foci in adults with epilepsy and it is reasonable to assume that many of the observations regarding reliability and validity of ESI in this particular setting may also apply to foci situated in other brain regions. It is likely, however, that recommendations derived from observations in this study of temporal lobe spike foci may not be applicable to widespread, bilaterally synchronous epileptiform discharges or to generalized spike and wave complexes, as such widespread synchronized cortical sources are unlikely to be amenable to noninvasive source localization, and likely to be subject to the severe limitations on ESI accuracy demonstrated in attempts to model the human K-complex (Wennberg and Cheyne, 2013; Chapter 6). Whether or not large unilateral extratemporal spike foci present problems similar to those associated with the bilaterally synchronous fields or may instead prove to be amenable to existing source localization techniques is an important question for future research in noninvasive source imaging.
The main recommendation to be derived from the results of this study is that ESI of single spikes should be avoided as a clinical tool. Spike averaging, ideally of at least 8 carefully selected topographically identical spikes – preferably more – should be performed prior to ESI whenever possible.

If individual spikes must be analyzed, the reliability and validity of source localization is improved through use of a LFF setting of at least 3 Hz. A 6 Hz LFF did not significantly improve upon the benefits seen with the 3 Hz LFF and in some situations was associated with more spurious results. LFF settings between 3 and 6 Hz were not tested in this study.

An important result of this ESI study was the demonstration that dipole source scatter is a reflection of the imperfect reliability of the source imaging methodology, and not an estimation of the extent of cortical epileptogenicity. The identification of single spike dipole source clusters might provide rough guidance to differentiate localization of a spike generator at the lobar level, e.g., frontal lobe versus temporal lobe. However, the observed dipole source cluster is related to fallibilities of the source localization technique when modeling single spikes – precise intralobar localization of the true focal spike source maximum cannot be derived from a cluster of scattered dipole sources. The ability to perform ESI on averages of carefully selected topographically identical spikes appears to be of prime importance with respect to obtaining precise intralobar localization of the sort that could provide real added value to clinical presurgical investigation.

The fifth study (Chapter 8), analogous to the fourth study but using MSI, was a reliability and validity analysis of the MSI results obtained when modeling a similarly large collection of identical temporal lobe spikes (Wennberg and Cheyne, 2014a). The anterolateral temporal neocortical spike focus that was examined in detail in this study was not ideally situated for MEG analysis because of its significant radial field component (Ahlfors et al., 2010a,b; Huiskamp et al., 2010), and the localization results confirmed previous observations that MSI performed on classical anterior temporal lobe spikes is associated with a tendency toward posterior displacement of the source solutions within the temporal lobe (Ebersole and Ebersole, 2010).
Dipole mapping and distributed source modeling solution maxima were both mislocalized posteriorly to a similar extent.

In contrast, MSI performed on mesiobasal temporal spikes from a focus that presumably presented a predominantly tangential current was able to provide accurate source localization, despite the relatively low amplitude of the extracranial spike field (Wennberg and Cheyne, 2014a; Chapter 8).

Notwithstanding the inability of MSI to provide a physiologically valid source localization of the anterior temporal spike focus, the reliability of the MSI methodology was testable in this study by looking for reproducibility of source localization results from one spike to the next, given that the true cortical source of each individual spike was known to be essentially identical (from intracranial recordings). In this regard, the observed scatter of source solutions obtained when modeling these identical spikes, as in the ESI study, demonstrated that the clustering of MSI dipole sources was due to limitations in reliability of the technique. It is possible that this finding may be relevant to the physiologic interpretation of most, if not all, clusters of scattered MSI dipole sources in patients with focal epilepsy. Qualitative analysis of dipole sources associated with this patient’s mesiobasal temporal spike focus showed the same limitations in reliability when modeling single spikes.

High goodness-of-fit values were associated with decreased scatter (i.e. improved reliability) as well as improved source localization validity (at the lobar level) when modeling individual spikes, although even source solutions with $V > 90\%$ were scattered quite widely throughout the temporal lobe (and a requirement for even higher goodness-of-fit, e.g., $V > 95\%$, would have excluded most spikes from the analysis). The proportion of spikes meeting reasonable goodness-of-fit values was increased and the reliability of source solutions improved when modeling single spikes with the use of a higher LFF setting (e.g., 3 Hz). As with ESI, reducing the power of low frequency background activity fluctuations and thereby increasing SNR is
presumably responsible for the slight improvement in reliability seen with a higher LFF when modeling individual spikes.

Unexpectedly, the single sphere forward model was associated with better reliability for MSI, particularly in terms of dipole source orientation, than the realistic head shaped BEM volume conductor. The reasons for this are unknown, particularly when a realistic head shaped BEM volume conductor was associated with very accurate dipole source localization and orientation attained when modeling the simultaneous 19 channel EEG data for the same spikes (Wennberg and Cheyne, 2014a). One can only speculate that the use of only a single conducting layer in the MEG BEM forward model resulted in an incorrect or biased correction for volume currents that degraded the overall solution, such that no correction provided better results.

As with ESI, signal averaging performed on increasing numbers of spikes significantly improved the reliability of source solutions and, once more than 8 spikes were averaged, removed any benefits of the higher LFF settings. The advantages of spike averaging presumably arise from the associated increase in SNR (Stephen et al., 2003; Van’t Ent et al., 2003; Bast et al., 2004, 2006), and most specifically from diminishing the power of the background noise in the MEG signal.

The findings of this MSI study pertain primarily to spikes arising from the anterolateral temporal neocortex, an area confirmed to contain brain regions for which MEG may lack sufficient sensitivity. Nonetheless, the observations on reliability likely have broader applicability and the demonstration that dipole source scatter may often be related to the limitations in reliability of the source localization techniques, rather than the extent of the underlying epileptogenic cortex, is an important observation with regard to the physiological interpretation of clusters of dipole sources.

If it is necessary to perform MSI on single spikes, it would appear that a LFF of 3 Hz or even 6 Hz is preferable to a more standard 1 Hz setting. It would also appear that a single sphere forward model may be sufficient for MSI.
As with ESI, spike averaging appears to be of paramount importance with regard to improving the reliability of source localization using MSI methodology. Averaging a minimum of 8 spikes is advisable and benefits continued to accrue with averages of 16, 32 and even 64 spikes with respect to decreased CE volume and improved SNR and goodness-of-fit values. It is of course imperative that only spikes arising from a well defined single spike focus are included in the averaging process, something which still requires careful analysis of the topographic spike fields by a clinical neurophysiologist prior to spike averaging. Further research into methods that may accurately classify subpopulations of topographically identical spikes in an automated fashion will be important in the continued development of MSI in epilepsy (Van’t Ent et al., 2003; Mohamed et al., 2013).

For both ESI and MSI, the anterior temporal spike results (regarding reliability and the benefits of spike averaging) appeared to be generalizable to different temporal lobe foci, whether situated anterolaterally, laterally (mid temporal) or mesiobasally (Wennberg and Cheyne, 2014a,b). Similar studies will need to be performed to determine whether the findings are applicable to spike foci in other brain regions. As an example of potential generalizability to other, similarly-sized foci, in this case involving the lateral convexity of a different lobe, Fig. 9.3 shows ESI results obtained from modeling a grand averaged (n = 64) spike waveform in an adult patient with right frontal lobe epilepsy. The patient has not come to surgery and no intracranial EEG is available for comparison, however, in Fig. 9.4 it can be seen that the ESI results, with respect to reliability, are similar to those described for the temporal lobe foci, and the averaged spike localization and orientation corresponds well with the surface topographic plot.
Fig. 9.1. Comparative results of EEG dipole mapping and distributed source modeling performed on (A) the spike of a single generalized spike and wave discharge, (B) the wave of the same generalized spike and wave discharge, and (C) a single K-complex. Same adult patient with primary generalized epilepsy as in Fig. 1.3. Dipole mapping, sLORETA and LORETA provide a similar deep midline source solution for each of the three entities. Volume conductor = FEM.
Figure 9.2

(A) Absence seizure (3 Hz generalized spike and wave) recorded with simultaneous MEG and EEG in a young adult patient with primary generalized epilepsy. (B) Averaged MEG waveform of 10 successive spike peaks from within absence seizure (spikes marked p1 in (A)) and associated dipolar magnetic flux topographic plot. (C) Distributed source modeling with sLORETA performed on the averaged MEG spikes in (B) provides a deep midline source solution, irrespective of solution subspace. Volume conductor = sphere calculated from MNI averaged brain MRI dataset. Solution subspace = cortex with fixed normal sources extended over a 20 mm patch (upper row) and whole volume 3D grid (lower row).
Fig. 9.3. (A) Averaged EEG waveform of 64 spikes recorded in an adult patient with right frontal lobe epilepsy and normal brain MRI. The interictal spikes were of low amplitude and showed an uncommon low amplitude transverse dipole with maximal electronegativity at F8 > F4, T4 > C4 and contralateral frontocentrotemporal positivity, as well as ipsilateral frontopolar (Fp2) positivity. (B) Dipole mapping and sLORETA modeling performed on the grand average of 64 spikes both provided right ventrolateral frontal source solution maxima consistent with the localization and orientation suggested by the surface voltage topographic plot. Volume conductor = BEM forward model created from patient’s own MRI. sLORETA solution subspace = cortex with fixed normal sources extended over a 20 mm patch.
Figure 9.4

A

Individual spikes 1-16  
Average 8 spikes (1-8, 9-16, ... 57-64)  

B

Average 64 spikes
Fig. 9.4. (A) Dipole mapping performed on 16 single spikes (left) and averages of 8 spikes (right) from the same right frontal focus described in Fig. 9.3. Spike averaging resulted in decreased scatter of source solutions (i.e., increased reliability), as seen with ESI performed on anterior temporal spikes. (B) Dipole source solution obtained for grand average of 64 spikes showing ventrolateral frontal localization and source orientation aligning well with the voltage topographic map. Volume conductor = BEM. LFF = 1 Hz.
Chapter Ten

Conclusions
CONCLUSIONS

The findings obtained in the various studies that make up this thesis give rise to a number of conclusions regarding the use of ESI and MSI for clinical and research studies:

**ESI and MSI of K-Complexes**

1. Large, extended superficial cortical sources pose special problems for noninvasive source localization, in particular, a propensity to deep midline source solutions
2. No combination of the tested forward and inverse (dipole and distributed source) models could resolve the propensity of the localization algorithms to return invalid deep midline solutions for the extended superficial cortical source
3. If accurate source localization is a requirement, current-generation ESI and MSI cannot be used to study large, bilaterally synchronous extended sources such as those responsible for K-complexes, sleep slow waves, and generalized spike and wave discharges

**ESI of anterior temporal spikes**

1. ESI of single spikes is limited by low reliability (scattered localization results for intracranially identical spikes); ESI of single spikes should be avoided as a clinical tool
2. Spike averaging, by reducing physiologic noise, significantly improves reliability and validity of source localization; for clinical purposes, at least 8 (preferably more) topographically identical spikes should be averaged prior to ESI
3. Averaged spike dipole source solutions are not necessarily localized deep to their superficial cortical generator
4. To acquire sufficient spikes to permit optimal spike averaging, prolonged recordings may be required; clinical video-EEG monitoring performed during routine presurgical investigation may be ideal for data collection.

5. Use of an individualized BEM forward model is optimal.

6. Modeling is best performed on the spike peak, where SNR is maximal.

7. Distributed solutions do not necessarily reflect the extent of epileptogenic cortex, as defined by the intracranial spike field (but are comparable to dipole sources in terms of reliability and validity for identification of cortical source maxima).

**MSI of anterior temporal spikes**

1. Selecting source solutions based on goodness-of-fit combined with filtering data at 3 Hz and above can result in reasonable reliability at the lobar level when modeling single spikes, but reliability at a finer level of localization is limited.

2. Reduction of background noise through spike averaging significantly improves the reliability of source solutions independent of goodness-of-fit or data filtering.

3. Averaged spike dipole source solutions for an anterolateral temporal neocortical focus are shifted posteriorly likely due to MEG-specific sensitivities to source orientation (in contrast, a mesiobasal temporal neocortical focus is associated with no spatial shift in dipole source localization).

4. Use of a sphere forward model is optimal.

5. Dipole source scatter does not reflect the extent of epileptogenic cortex.
Chapter Eleven

Future Directions
The source imaging results presented in this thesis showed ongoing difficulties with attempts to accurately localize very large extended cortical sources. However, cortical sources of more moderate size in the temporal lobe proved to be quite amenable to source modeling, with lobar accuracy a realistic expectation when modeling single spikes and a much finer degree of sublobar accuracy possible when modeling averaged spikes. Although much work remains to be done, it is clearly a testament to how far the fields of ESI and MSI have advanced that we are able, in the right setting, to solve the inverse problem with this degree of accuracy.

Nonetheless, there is a need to achieve even better, more consistent, and more widely applicable localization results in the future. Rigorous studies of the sort presented in this thesis, comparing source imaging solutions with their actual intracranial fields, represent a logical and necessary progression in electromagnetic source imaging research. Some obvious questions present themselves as subjects for next stage studies on the application of ESI and MSI to human sleep potentials and epileptiform discharges. In addition, recent advances facilitating the simultaneous recording of MEG and intracranial EEG (Taulu and Hari, 2009; Airaksinen et al., 2011; Jin et al., 2013) will permit direct comparison of MSI results with simultaneously acquired intracranial EEG field data.

**Determination of the size of an extended cortical field at which the propensity to false, deep source localization begins**

Future research will be needed to determine the size of an extended cortical field at which the propensity to false, deep source localization begins. Can “large enough” unilateral sources be responsible? Or is the propensity toward deep mislocalization seen only with bilateral sources?

Fig. 11.1 shows preliminary results obtained with ESI applied to a large unilateral extended cortical source responsible for the generation of very high amplitude spike and wave
discharges in a patient with right frontal lobe epilepsy (patient 4 in Wennberg, 2010b; Wennberg and Cheyne, 2013). The intracranial cortical source extended to involve synchronously the anterior, lateral and inferior aspects of the right frontal lobe, sparing only the mesial frontal region and the most medial aspects of the frontopolar and orbitofrontal cortices. The dipole source solution, however, was situated in the orbitofrontal region deep to the superficial midfrontal lateral cortical source maximum most responsible for the high amplitude EEG spikes. These findings suggest that a very large unilateral source may be subject to some of the same problems seen with attempts to model the K-complex and generalized spike and wave discharges, as has been suggested previously in computer simulations (Kobayashi et al., 2005).

The sort of analysis presented in Fig. 11.1 would of course need to be extended to the same degree of detail explored in the ESI and MSI studies that made up this thesis, investigating a greater number of spikes, and similarly studying the effects of different filters, forward and inverse models, as well as examining the same spikes with MSI.

Questions as to whether or not deep mislocalization is related simply to the size of the extended cortical source, e.g., as measured in square centimeters, or whether there may be a separable component related to the amplitude of the extracranial potentials, and whether or not involvement of more than one surface plane is important (e.g., the frontal lobe cortical source in the patient whose spikes are depicted in Fig. 11.1 “wrapped around” the dorsal, lateral, anterior and ventral planes), all remain to be answered. Computer simulation studies may prove especially useful for continued research into the latter question.

Construction of a catalogue of sleep transients and spike foci and their corresponding ESI and MSI results

It will be important to construct a catalogue of ESI and MSI localizations attributable to electromagnetic potentials generated by extended sources of different sizes and locations in the brain.
In the case of sleep transients, e.g., vertex waves, sleep spindles, positive occipital sharp transients of sleep (POSTS), and slow waves of deep non-REM sleep, as with K-complexes, the cortical source generators are expected to be the same in all individuals (barring significant structural abnormality or cortical dysfunction). As such, detailed studies performed on relatively small numbers of subjects should prove informative. Accurate determination of the superficial cortical areas responsible for generating these sleep transients will be highly useful for future studies of sleep physiology.

Unlike sleep, spikes in human epilepsy may arise from multiple different foci in varying locations with individual specificity. Nonetheless, the different lobes of the brain may be isolated for independent study and representative examples of spikes from the different parcelations examined against their corresponding intracranial fields, which will identify particularities of ESI and MSI in relation to different brain regions.

Such a catalogue constructed over time to contain representative spike foci and their associated topographic fields, from the largest, generalized, and bilaterally synchronous distribution to the smallest extracranially resolvable lateralized distribution could serve as an encyclopedic aid to the interpretation of noninvasive source localization results for purposes of clinical diagnosis and presurgical planning in epilepsy, and eventually help to obviate the need for intracranial EEG monitoring in many patients.

The inclusion of both MSI and ESI solutions for identical spikes generated in the same brain regions, in the same patients, would be invaluable as an aid for interpretation of MSI results, given the known sensitivities to source orientation particular to MEG. A catalogue of this information would serve as a reference to predictable differences between MSI and ESI localizations (such as the posterior shift for MEG dipole sources when modeling anterior temporal spike foci, as seen in this thesis (Wennberg and Cheyne, 2014a,c; Chapter 8; Appendix 2) and as described previously (Ebersole and Ebersole, 2010). The emerging ability to perform simultaneous MEG and intracranial EEG will greatly facilitate this pursuit in the future.
Fig. 11.1. Averaged EEG waveform of 17 high amplitude right frontal spike and wave discharges recorded in an adult patient with right frontal lobe epilepsy and normal brain MRI (patient 4 in Wennberg, 2010b; Wennberg and Cheyne, 2013). The interictal spikes were of high amplitude and showed maximal electronegativity at F4 (left; LFF 0.5 Hz, HFF 70 Hz). Subsequent stereoelectroencephalographic investigation showed these spikes to have a diffuse neocortical generator involving synchronously the lateral, inferior and anterior frontal cortex, sparing the mesial frontal region as well as the most medial aspects of the frontopolar cortex and orbitofrontal cortex. Dipole mapping performed on the averaged spike (n = 17) returned a deep ipsilateral orbitofrontal source solution (right; Volume conductor = FEM; LFF 1 Hz, HFF 30 Hz).
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Appendix 1

On electrical potentials observed at a distance
from intracranial electrode contacts

Previously published as:

Wennberg, R.
On electrical potentials observed at a distance from intracranial electrode contacts.
On electrical potentials observed at a distance from intracranial electrode contacts

I read with interest the paper of Zaveri et al. (2009), which argued for the position that an electrical potential at a distance cannot be observed by an intracranial electrode contact. I cannot attempt to refute the mathematical arguments explaining the magnitude of electrical field intensity due to a point charge, and indeed these arguments seem to align well with everyday clinical observations of electrical potentials generated by small fields in the brain.

However, I am not so sure that this line of argument holds for electrical potentials generated by large fields in the brain – the size of the field may actually matter here. Zaveri et al. (2009) state that their position holds equally well for single point charges and spatially extended electrical fields, but I believe this requires further consideration. Rather than (and incapable of) providing a mathematical counter argument, I would like to present for consideration instead a series of EEG pictures showing what an intracranial electrode contact observes at the time of a large distant electrical discharge in the brain, because the pictures do seem to show adjacent intracranial electrode contacts observing synchronously, at a distance, volume conducted cerebral electrical potentials.

We have previously reported on volume conducted cortical epileptiform and sleep potentials observed by intracranial electrode contacts in the thalamus (Wennberg et al., 2002; Wennberg and Lozano, 2003). In referential montages, the large distant cortical potentials were observed with zero time-delay and inverted polarity by the thalamic electrode contacts, with a small but reproducible amplitude decrement present at each electrode contact more distant from the cortical source. The amplitude of the inverted (positive) intrathalamic waveforms showed a direct, and approximately linear, correlation with the amplitude of the distant surface negative cortical electrical potentials (Wennberg and Lozano, 2003). The figures presented here extend those observations to electrode contacts situated elsewhere in the brain.
**Interictal epileptiform potentials (spikes)**

As mentioned above, the argument put forth by Zaveri et al. (2009) seems perfectly applicable to the great majority of focal intracranial spikes that have no representation on scalp EEG due to their insufficient field size. However, the situation may differ when spikes are generated by larger neocortical fields, such as those capable of producing visible waveforms in the scalp EEG, a circumstance known to require synchronous activity involving at least 6 cm² (Cooper et al., 1965) or, more frequently, 10-20 cm² of cortex (Tao et al., 2007).

As shown in Fig. 1, spikes of this size do produce a visible volume conducted electrical field, which is inverted in polarity (with respect to the surface negative neocortical generator), and which appears with zero time-delay at distant adjacent intracranial electrode contacts, including those situated within subcortical white matter. For these spikes generated within the anterior and (to lesser extent) basal lateral temporal neocortex, the lower amplitude volume conducted waveforms appear posteriorly and inferomesially, observed by the electrode contacts situated behind and below the anterior temporal cortical dipole layer source. Although evident in the individual traces, averaging of the spikes makes the volume conduction more apparent by diminishing the independent background activity observed by the different intracranial electrode contacts (Fig. 1).

**K-complexes**

The K-complex is the highest amplitude graphic element in the human EEG, and thus provides an extreme example of a large, spatially extended electrical discharge in the brain. What is observed at a distance from intracranial electrode contacts in the case of K-complexes?

Here again, as shown in Figs. 2 and 3, inverted (positive) waveforms are seen by distant adjacent electrode contacts with zero time-delay, including contacts within the white matter of the frontal lobe and temporal lobe, locations one may confidently assume have no active role in K-complex generation. Compared to the temporal lobe spikes, more remote intracranial electrode
contacts may observe the volume conducted K-complex field, in keeping with its greater surface spatial extent. As with the temporal lobe spikes, averaging of the individual K-complexes makes the volume conducted component of the intracranial field more apparent.

Based on the visual evidence, it seems that intracranial electrode contacts do sometimes observe distant electrical potentials. The main predictive feature of distant observation appears to be the size (amplitude and, especially, spatial extent) of the electrical field in question, which of course varies immensely between the different physiological and pathophysiological sources of electrical activity in the human brain. As such, the electrical potentials observed by intracranial electrode contacts might be best considered to represent a combination of local (“point”) sources and distant (“volume-conducted”) sources, the latter sometimes observable and sometimes not.

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Fig. 1. Stereoelectroencephalographic recordings obtained during presurgical clinical investigations in a patient with medically intractable epilepsy, bilateral independent temporal lobe spikes, right occipital lobe spikes and right occipital encephalomalacia. Shown from left to right are 5 individual right anterior temporal spikes arising from the anterior temporal neocortex, followed by an average of the 5 spikes. The spikes are clearly visible in the scalp EEG with maximal amplitude at F8, F10, Sp2, greater than T4, T10, appearing maximal intracranially over the anterior temporal neocortex (subdural electrode contacts TA1-4), the surface negative field extending to involve the basal lateral aspect of the anterior temporal lobe (subdural electrode contact TB4). Lower amplitude positive waveforms appear synchronously at the depth electrode contacts in the white matter and limbic region of the temporal lobe (TD1-4) and at the subdural electrode contacts overlying the basal mesial temporal cortex (TB1,2), the inverted polarity suggesting that contacts TD1-4, TB1 and TB2 are “seeing” the opposite, positive, side of the volume conducted electrical potential generated by the dipole layer identified within the anterior
temporal neocortex. MR images show the positions of intracranial 4-contact subdural electrodes overlying the anterior temporal (TA1-4, contact 1 most mesial), basal temporal (TB1-4, contact 1 most mesial) and posterior temporal (TP1-4, contact 1 most posterior) neocortices, as well as an orthogonally implanted 4-contact depth electrode aimed at the anterior hippocampus (TD1-4, contact 1 most mesial). Common average reference montage for both scalp and intracranial EEG, the average reference comprising 12 scalp electrodes (F3, F4, C3, C4, P3, P4, O1, O2, T3, T4, T5, T6); LFF 0.5 Hz, HFF 70 Hz, all figures.
Figure 2

Fig. 2. Same patient as Fig. 1. Shown from left to right are 5 individual K-complexes recorded during stage 2 sleep, followed by an average of the 5 K-complexes. The frontally predominant surface negative K-complexes visible in the scalp EEG appear synchronously, with inverted polarity, at the distant intracranial electrode contacts within and on the surface of the temporal lobe, consistent with downward volume conduction of the large distant superior frontal electrical potential.
Figure 3

Fig. 3. Stereoelectroencephalographic recordings obtained during presurgical clinical investigations in a patient with medically intractable right frontal lobe epilepsy, normal brain MRI, inactive frontal spikes. Shown from left to right are 5 individual K-complexes recorded during stage 2 sleep, followed by an average of the 5 K-complexes. The large, high amplitude frontally predominant surface negative K-complex visible in the scalp EEG appears maximal intracranially over the superior frontal neocortex (subdural electrode contacts FL1 and FL2), the large frontal surface negative cortical dipole layer source decreasing in amplitude anteriorly and inferiorly. The intracranial depth electrode contacts situated within the white matter of the frontal lobe (FD1-4) observe synchronously the positive side of this extended frontal lobe dipole layer, the positive K-complex waveforms in white matter representing posterior and downward volume conduction of the large surface negative field generated in the surrounding frontal cortices. MR
images show the positions of intracranial 4-contact or 6-contact subdural electrodes overlying the lateral frontal (FL1-4, contact 1 most superior), medial frontal (FM1-4, contact 4 most superior) and anterior frontal (FA1-6, contact 1 most medial) neocortices, as well as a superior-to-inferior 4-contact depth electrode implanted through the superior frontal gyrus (FD1-4, contact 1 most inferior).
Appendix 2

Elucidating the meaning of dipole variability in MEG/MSI

Published previously as:

Wennberg, R. and Cheyne, D.
Elucidating the meaning of dipole variability in MEG/MSI.

Authors’ response to:

Bagić, A. and Ebersole, J. S.
Does MEG/MSI dipole variability mean unreliability?
Elucidating the meaning of dipole variability in MEG/MSI.

In their letter to the Editor, Bagić and Ebersole (2014) outline a number of criticisms of our recent publication (Wennberg and Cheyne, 2014a) with regard to the use of the term \textit{reliability}, and more specifically our claims about the ability to consistently replicate source locations for what we had identified as “identical” spike sources. They also raise concerns about the implications of our conclusions on the reliability of MSI in general (Bagić and Ebersole, 2014). With respect to “reliability”, as we defined it in the introduction of our paper (Wennberg and Cheyne, 2014a), we used this term in a practical sense to refer to the ability to reliably obtain a similar source solution for what we could ascertain as spikes arising from the same brain location. We ourselves had attached no emotional valence to the word, but now realize we were unmindful of potential sensitivities associated with its use. Accuracy or consistency might arguably have been used as synonyms; however, accuracy suggests not only consistency, but also validity (which was studied separately). In the end, reliability was chosen as the counterpart of validity in scientific parlance. We certainly had no intent in choosing our terms to appear negative toward MEG inverse modeling in general. A dispassionate reading of our article should reveal only a desire to increase understanding in the field and, hopefully, to contribute to continued advances.

With respect to their claim that we were misleading in the use of the term “identical” spikes, it is true that absolute identicality is not what existed between the different spikes studied. In places, we used the phrase “essentially identical” to mean as similar as possible within the limits of the measures used. In this spirit, we had aimed for full transparency by providing detailed figures of the intracranial EEG waveforms of the anterior temporal lobe spikes that formed the basis of the investigations presented in our MEG/MSI and EEG/ESI papers (Wennberg and Cheyne, 2014a,b). Perhaps a term such as “highly similar” would be less contentious, but also more vague, and in the end the term identical was chosen to indicate that, for
all clinical intents and purposes, the spikes under investigation could be viewed as arising from
the same anterolateral temporal neocortical “focus”, with the conviction that the ultimate goal of
source modeling should be to accurately identify such a focus “at a level of localization better
than what [a clinical neurophysiologist] can surmise by simply looking at the raw data”
(Wennberg and Cheyne, 2014b).

It is clear that physiological variability prevents any two spikes from being identical in
the strict sense of the term. Intracranial EEG recordings in patients with mesial temporal lobe
epilepsy show marked variations between spikes in terms of morphology, amplitude, and
intralobar localizations, as pointed out by Bagić and Ebersole (2014). However, for our studies,
we specifically selected “essentially identical” spikes from a given spike focus to use as a tool to
assess the accuracy of our source modeling procedures. In this regard, we feel that their assertion
that the selected anterior temporal lobe spikes may have been “far from identical” is not
supported. As further evidence, and to clarify our criteria for identicality, we provide here a
longer segment of recording than shown in our papers. Fig. 1 depicts 20 seconds of continuous
stereoelectroencephalographic (simultaneous intracranial and scalp EEG) recording obtained in
the patient whose results were presented in (Wennberg and Cheyne, 2014a,b). One can identify
many independent intracranial spikes, of different amplitudes and in different locations, but one
can also see that there are three “essentially identical” high amplitude spikes, each associated
with a synchronous right anterior temporal spike visible on the scalp EEG.

More than 200 hours of continuous stereoelectroencephalographic recording performed
in this patient showed that all extracranially visible right anterior temporal scalp EEG spikes were
associated with the same “essentially identical” intracranial spike field demonstrated in Fig. 1 (as
well as in Fig. 1 of (Wennberg and Cheyne, 2014a) and in Fig. 2 and Supplementary Figs. S1-S3
of (Wennberg and Cheyne, 2014b)). Examination of the intracranial EEG waveforms associated
with these right anterior temporal spikes does not in fact suggest that a number of these spikes are
“far from identical”. On the other hand, examination of the simultaneously acquired scalp EEG
waveforms does reveal obvious differences in the appearances of the extracranially recorded spikes. But this gets to the crux of the problem. How are we to be able to accurately determine, through inverse modeling of these different extracranially recorded spike potentials, their common, spatially restricted intracranial source? As we concluded, the single best option currently available to optimize the accuracy of our inverse modeling is to average large numbers of “essentially identical” spikes, thereby reducing background noise, which appears to be a key determinant of dipole scattering. On this most important point, we are in full agreement with Bagić and Ebersole (2014).

In a seminal paper describing the intracranial EEG substrates of scalp EEG spikes, Tao et al. (2005) investigated spikes originating from the lateral and inferolateral aspect of the anterior temporal lobe (Tao et al., 2005). In Fig. 2A we show representative examples of the right anterior temporal scalp EEG spikes recorded in the patient described in (Wennberg and Cheyne, 2014a,b) and in Fig. 2B we show a left anterior temporal spike as presented in (Tao et al., 2005). The EEG waveforms and their associated field maps are highly similar, with maximal electronegativity coalescing between F7/8 and F9/10 and a corresponding, broader region of electropositivity over the contralateral centroparietal area. The intracranial cortical source maximum in the patient described in (Tao et al., 2005) is evident over the lateral aspect of the anterior temporal lobe (Fig. 2B). In Fig. 2C we show in more detail the EEG field maps obtained from 19 and 27 electrode data sets, and show also how the simple “top down” topographic map of the 19 channel EEG – notwithstanding its limitations – can provide very useful information regarding spike similarity.

Against the backdrop of these observations, we cannot agree with Bagić and Ebersole (2014) that the right anterior temporal spikes we studied represented a “temporal tip” focus with a tangential orientation advantageous for MEG study. Firstly, our intracranial EEG data showed the cortical spike maximum to be situated well lateral to the tip of the temporal pole, and the electrical field extended further laterally away from the focal maximum, as described in detail in our Methods section and as shown in Fig. 1 and Supplementary Fig. S1 of (Wennberg and
Secondly, as described above, our anterior temporal spike focus appears to be highly similar to one described previously and shown, using detailed intracranial EEG analysis, to be entirely localized to the lateral and inferolateral aspect of the anterior temporal lobe (Tao et al., 2005). Lastly, a significant radial, not tangential, field component of this spike focus actually made it not ideal for MEG study, and presumably contributed to the posterior displacement of the MEG dipole source localizations (Fig. 2C), a finding previously described to be common with MSI of temporal lobe spikes (Ebersole and Ebersole, 2010). The first three paragraphs of our Discussion dealt specifically with this issue (Wennberg and Cheyne, 2014a).

We did not discuss dipole scattering with ESI because, as we stated in the Methods (Wennberg and Cheyne, 2014a), that was the subject of a separate paper (Wennberg and Cheyne, 2014b). In fact, comparisons between MSI and ESI were not a thrust of either paper. We also did not imply that our results reflected any fundamental limitations of source analysis using MEG or EEG, as might have been interpreted from our statement that dipole variability may be related to “limitations in the spatial accuracy of the source localization technique”. In this regard, we assume that variability as discussed here is related primarily to physiological noise, and not to any spatial resolution inconsistency inherent in the modeling algorithms. The latter would be better demonstrated through simulations and analysis of modeling errors. These issues are being increasingly addressed within the MEG/EEG research community for assessing the spatial accuracy of various inverse methods (e.g., Hauk et al., 2011; Hauk and Stenroos, 2014) but have yet to be fully studied in cases of spike localization.

In their letter, Bagić and Ebersole (2014) suggest that limitations in reliability of MSI might have been better demonstrated had we shown that minor variations in spike parameters resulted in inconsistent and “unusually large” variations in dipole locations. As an example of this sort of analysis, Fig. 3 shows the results of MSI performed on 4 separate spikes, each differing slightly in terms of topography or amplitude. Despite the high goodness-of-fit values for each of
the source solutions, the dipole localizations are scattered rather unpredictably within the temporal lobe.

It is perhaps a testament to how far the field has advanced that we are able to solve the inverse problem with even this degree of lobar accuracy. But it is not unreasonable to attempt to achieve even better, more consistent, localization results. Rigorous studies comparing dipole source solutions with their actual intracranial fields represent a logical and necessary progression in electromagnetic source imaging research. Recent advances facilitating the simultaneous recording of MEG and intracranial EEG promise even greater insights into the nature of dipole variability in MEG/MSI.

References


Fig. 1. Twenty second segment of stereoelectroencephalographic recording obtained in patient presented in (Wennberg and Cheyne, 2013a,b). Intracranial EEG (top) shows multifocal independent spikes, most of which have no representation in the extracranial, scalp EEG (bottom). Each of the three visible right anterior temporal lobe scalp EEG spikes (phase reversals at F8, F10; (*)) is associated with an essentially identical high amplitude intracranial spike localized to the anterolateral temporal neocortex (RTA2 > RTA3 > RTA1). Two high amplitude intracranial spikes localized to this patient’s left mesiobasal focus (LTB1, LTB2 > LTB3 >
LTB4; described in Wennberg et al., 2011) are barely discernable in the scalp EEG (^). L = left; R = right. MRI insets show intracranial 4-contact subdural electrodes overlying the anterior temporal (TA1-4, contact 1 most anterior), basal temporal (TB1-4, contact 1 most mesial) and posterior temporal (TP1-4, contact 1 most posterior) neocortices, as well as an orthogonally implanted 4-contact depth electrode aimed at the anterior hippocampus (TD1-4, contact 1 most mesial). Common average reference for intracranial EEG, comprising 12 scalp electrodes (F3, F4, C3, C4, P3, P4, O1, O2, T3, T4, T5, T6); LFF 0.5 Hz, HFF 70 Hz.
Fig. 2. (A) Three anterior temporal spikes and their associated 27 channel EEG voltage topographic plots, from the same patient’s stereoelectroencephalographic study (spikes 53, 17 and 57 in Wennberg and Cheyne, 2013b). (B) A left anterior temporal spike (left), its associated 26 channel EEG voltage topographic plot (middle), and the cortical distribution of its intracranial EEG field (right), obtained using a combination of scalp EEG, subdural grid and subdural strip electrodes in a different patient with temporal lobe epilepsy, as described previously by (Tao et al, 2005). The scalp EEG waveforms and topographic plots are comparable to those of the spikes shown in (A). The active intracranial electrode contacts (black and colored circles) extend over the anterolateral and inferolateral aspect of the temporal lobe; contacts showing highest spike amplitude marked in red and blue (from Fig. 6 in Tao et al., 2005, color added to original; used with permission, John Wiley and Sons). (C) Comparison of EEG voltage topographic plots of an anterior temporal spike (spike 4 in Wennberg and Cheyne, 2013b) with and without inclusion of subtemporal EEG electrodes (F9/10, T9/10, P9/10, Sp1/2) shows loss of resolution of the
electronegative field maximum when only 19 electrodes are included (middle), as compared to the 27 channel recording (left). For this particular spike, the dipole source solution was shifted posteriorly when modeled using 19 EEG electrodes (curry) as compared to 27 EEG electrodes (green). Despite the inability to completely resolve electronegative field maxima in the 19 channel EEG recordings obtained during the MEG study, comparison of the 19 channel EEG maps constructed from the stereoelectroencephalographic data (middle) with those obtained during the MEG/EEG study (right) readily facilitated selection of comparable right anterior temporal spikes. For this particular MEG spike (spike 43 in Wennberg and Cheyne, 2013a), the MEG dipole source solution (magenta) was situated posterior to the EEG dipole source solution (curry), as is common for temporal lobe spikes (Ebersole and Ebersole, 2010). Volume conductor = BEM for EEG, sphere for MEG. LFF 3 Hz, HFF 30 Hz.
Fig. 3. MEG spike waveforms, magnetic flux fields and EEG voltage topographies of 4 right anterior temporal spikes (top), selected from among the 64 spikes presented in (Wennberg and Cheyne, 2013a). Dipole source solutions for the 4 spikes (bottom), each with goodness-of-fit > 90%. For temporal neocortical spikes, there is a direct correlation between intracranial and extracranial amplitude (Wennberg and Lozano, 2003); nonetheless, minimal variations in spike amplitude between spikes 12, 52 and 11 were associated with considerable variability in dipole localizations. In contrast, very similar dipole localizations were returned for spikes 12 and 34, whose amplitude and MGFP differed considerably. V = explained variance. MGFP = mean global field power. LFF 3 Hz, HFF 30 Hz, sphere volume conductor.