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On noninvasive source imaging of the human K-complex

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HIGHLIGHTS

- Large, extended superficial cortical sources may pose special problems for noninvasive source localization, in particular, a propensity toward deep midline source solutions.
- Various EEG and MEG source imaging techniques were applied to model the human K-complex, and source solutions were compared with the intracranial cortical localization.
- 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.

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.

1. Introduction

The application of EEG and MEG source imaging to the human K-complex has produced conflicting and occasionally implausible

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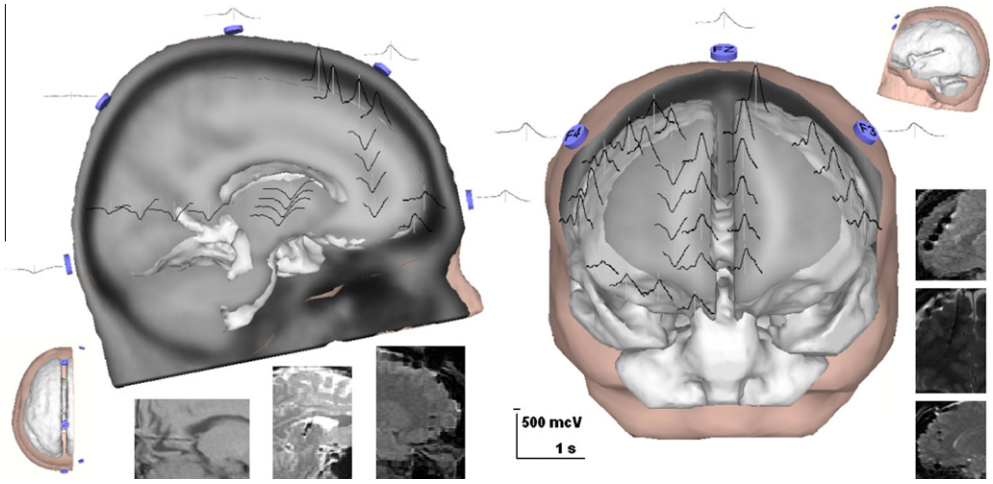

Fig. 1. Composite diagram of averaged EEG K-complex waveforms recorded in patients from scalp, frontal lobe cortex, frontal lobe white matter, thalamus, and medial occipital lobe. Surface negative scalp EEG peak maximal at Fz > F3, 4 > Cz corresponds to synchronous surface negative intracranial peak 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 and 6–9 in Wennberg, 2010).

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, 2010). 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, 2010). 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. 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, 2010). 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, 2010). 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)