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Invariance in current dipole moment density across brain structures and species: Physiological constraint for neuroimaging

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ABSTRACT

Although anatomical constraints have been shown to be effective for MEG and EEG inverse solutions, there are still no effective physiological constraints. Strength of the current generator is normally described by the moment of an equivalent current dipole ***Q***. This value is quite variable since it depends on size of active tissue. In contrast, the current dipole moment density *q*, defined as *Q* per surface area of active cortex, is independent of size of active tissue. Here we studied whether the value of *q* has a maximum in physiological conditions across brain structures and species. We determined the value due to the primary neuronal current ($q_{primary}$) alone, correcting for distortions due to measurement conditions and secondary current sources at boundaries separating regions of differing electrical conductivities. The values were in the same range for turtle cerebellum (0.56–1.48 nAm/mm^2), guinea pig hippocampus (0.30–1.34 nAm/mm^2), and swine neocortex (0.18–1.63 nAm/mm^2), rat neocortex (~2.2 nAm/mm^2), monkey neocortex (~0.40 nAm/mm^2) and human neocortex (0.16–0.77 nAm/mm^2). Thus, there appears to be a maximum value across the brain structures and species (1–2 nAm/mm^2). The empirical values closely matched the theoretical values obtained with our independently validated neural network model (1.6–2.8 nAm/mm^2 for initial spike and 0.7–3.1 nAm/mm^2 for burst), indicating that the apparent invariance is not coincidental. Our model study shows that a single maximum value may exist across a wide range of brain structures and species, varying in neuron density, due to fundamental electrical properties of neurons. The maximum value of $q_{primary}$ may serve as an effective physiological constraint for MEG/EEG inverse solutions.

Introduction

Anatomical constraints are informative in neuroimaging research. It is well known that the estimation of cortical activity based on inverse solutions of magnetoencephalography (MEG) or electroencephalography (EEG) data is not unique (cf. Hämäläinen et al., 1993). Such constraints have been shown to be effective in constraining the inverse solutions. A practical approach is to let neural generators of MEG and EEG signals be confined within the cortical mantle and to further constrain the sources to be oriented perpendicular to the cortical surface (Dale and Sereno, 1993; Dale et al., 2000). Very few studies have, however, thus far used physiological constraints for solving the inverse problem.

We report here one constant that may prove to be an effective physiological constraint in solving the inverse problem. In MEG and EEG, the current generator is described by an equivalent current dipole ***Q***. Its moment Q is customarily expressed in units of nAm. The moment is quite variable, varying by as much as three orders of magnitude, across many experimental conditions. The density *q* is defined as $q = Q / \theta$ in units of nAm/mm^2, where θ is the surface area of the active cortical volume. Since this density is independent of size of active tissue, it is more uniform than *Q* and may serve as a physiological constraint.

The value of *q* has been estimated from an estimate of moment *Q* determined experimentally and an estimate of the cross-sectional area θ (e.g. turtle cerebellum — Okada and Nicholson, 1988; Okada et al., 1989; guinea pig hippocampus — Murakami et al., 2002, 2003; swine neocortex — Okada et al., 1996; and monkey visual cortex — Lü and Williamson, 1991). The straightforward method of estimating *q* according to this definition is problematic because it does not necessarily estimate the $q_{primary}$ strictly due to neuronal currents. The value of *q* may differ from the value of $q_{primary}$ because measured MEG signals may be reduced by the finite size of the detection coil and distorted by the so-called secondary sources that are present at each boundary surface separating regions of differing electrical conductivities (Geselowitz, 1970; Geselowtitz, 1973; Grynszpan and Geselowitz, 1973; Plonsey, 1972). Thus, these possible effects must be taken into account in order to estimate $q_{primary}$ itself. These possible distortions have been known for a long time, but most studies have reported the uncorrected

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empirical values. We asked whether the range of $q_{primary}$ is smaller and more uniform than the range of q across the brain structures when these distortions are removed.

We found a remarkable level of uniformity in mean and maximum values of $q_{primary}$ across the neocortex of swine, the hippocampus of guinea pig and the cerebellum of turtle in the experiments carried out in our laboratory. These values matched the value of $q_{primary}$ previously computed for the monkey visual cortex by Lü and Williamson (1991). We then estimated $q_{primary}$ in the neocortex of rat and human based on previous MEG studies by others. These comparisons for the first time showed that the $q_{primary}$ is remarkably invariant in the 6-layer neocortex of rat, monkey, pig, and man. Moreover, they were similar to those for the 3-layer hippocampus of guinea pig and cerebellum of turtle.

These results motivated us to test whether the uniformity of $q_{primary}$ was coincidental or represents an invariance due to fundamental electrophysiological properties of neurons. We tested this question using a mathematical neural network we previously validated on an independent set of data (Murakami et al., 2002, 2003). Significantly, we found that the maximum empirical values of $q_{primary}$ quantitatively matched the theoretical maximum values of $q_{primary}$ under a few simplifying assumptions. This was obtained without any manipulations of the model parameters previously estimated from an independent set of empirical data, suggesting that the empirically observed invariance reflects conservation in fundamental electrophysiological properties of neurons.

The uniformity of $q_{primary}$ led to a question of whether this invariance is due to a conservation of a more fundamental quantity, namely metabolic energy consumption in neuronal tissues. Metabolic energy is required to repolarize the transmembrane potential after the initial depolarization during neuronal activity. The restoration of imbalance in intracellular concentrations of Na–K ions requires consumption of adenosine triphosphates (ATPs). The NaK-ATPase is responsible for most of the cell's energy expenditure (Hasenstaub et al., 2010; Laughlin and Sejnowski, 2003; Attwell and Laughlin, 2001; Laughlin et al., 1998). We conjectured that this uniformity of $q_{primary}$ reflects the conservation of energy consumption during the evolutionary process to protect the brain of different species during neuronal processing. We used the same simple model above with the same set of simplifying assumptions to test a hypothesis as to whether the number of ATPs consumed per cross-sectional area of a cortical tissue per unit time (ATP/mm^2 s) is invariant of cell size and density as for $q_{primary}$.

This report then has three parts: (1) our meta-analysis of empirical values of $q_{primary}$ and finding of an apparent invariance of maximum $q_{primary}$ due to primary neuronal currents; (2) a theoretical analysis of the basis for this result and finding of a quantitative match of the empirical and theoretical values of maximum value of $q_{primary}$; and (3) a theoretical study of variation in metabolic energy consumption per single burst of synchronized population activity with cell size and density and finding that the energy consumption decreases inversely with cell radius/density. We discuss the significance of these results for neuroimaging.

Materials and methods

Empirical analysis of current dipole moment density $q_{primary}$

Experimentally determined values of the current dipole moment density q were used to estimate the value of $q_{primary}$. Here we briefly describe our methods for estimating $q_{primary}$. The Appendix presents the details of our method and describes the specific procedures for correcting for these two types of distortion in the three preparations we have studied — in vitro turtle, in vitro guinea pig hippocampus and in vivo pig neocortex. In this text throughout, the variables in bold face refer to vector quantities and those in plain face refer to scalar quantities. Appendix Table 2 provides the definitions of all the symbols used in this paper for clarity.

Attenuation of actual field by finite size of magnetic field detection coils

The magnetic field $\boldsymbol{B}$ is commonly measured with a superconducting detection coil of a finite radius when the measurements are based on an MEG system using superconducting quantum interference devices (SQUIDs). The $\boldsymbol{B}$ field threads through the plane of the coil and introduces a change in current within the coil, which is detected by a SQUID inductively coupled to the coil. Thus, a finite-size detection coil measures a spatial average of the $\boldsymbol{B}$ field, attenuating the peak field. This attenuation effect has been analyzed by Williamson and Kaufman (1981) for current dipoles; they calculated the attenuation as a function of radius of the detection coil and depth of the dipole below the sensing surface. The equation for this correction is presented in the Appendix for the benefit of the readers since the above reference is not easily available. We used Fig. 6 in their publication to estimate the actual strength of the $\boldsymbol{B}$ field in each preparation. Jazbinšek et al. (1989) carried out a similar calculation for higher poles.

Distortion by secondary sources at conductivity boundaries

The $\boldsymbol{B}$ field measured outside a volume conductor is a sum of the $\boldsymbol{B}_{primary}$ field produced by a neuronal tissue of interest and the $\boldsymbol{B}_{secondary}$ field due to each conductivity boundary separating two conductive media of differing electrical conductivities. The single equivalent current dipole responsible for $\boldsymbol{B}_{primary}$ is denoted as $\mathbf{Q}_{primary}$. Each source of $\boldsymbol{B}_{secondary}$ field at each boundary is called secondary source; this source can be represented by a single equivalent current dipole $\boldsymbol{Q}_{secondary}$ (Huang et al., 1990). Each $\boldsymbol{Q}_{secondary}$ is directed perpendicular to the boundary surface: $\boldsymbol{Q}_{secondary} = V\Delta\sigma d\boldsymbol{S}$, where V is the potential on the surface with a surface vector $d\boldsymbol{S}$ and $\Delta\sigma = \sigma_{region\ 1} - \sigma_{region\ 2}$ is the difference in conductivity across the boundary surface separating two regions with the $\mathbf{Q}_{primary}$ in region 2 and $d\boldsymbol{S}$ is the surface normal (Plonsey, 1972, 1981). We have previously computed the strength of $B_{secondary}$ relative to the $B_{primary}$ as a function of $\Delta\sigma$ and distance between $\mathbf{Q}_{primary}$ and a given boundary (Huang et al., 1990). The estimates are based on a boundary element method (BEM) analysis of the conductivity geometry of a turtle cerebellum in a bath. We used the parametric results in Fig. 7 of our previous work (Huang et al., 1990) to estimate $Q_{secondary}/Q_{primary}$.

All the tissues were assumed to be homogeneous in electrical conductivity. Previously, we have experimentally determined the tissue conductivity in the turtle cerebellum and found that the extracellular conductivity σ_e along the depth is inhomogeneous (0.25 ± 0.05 S/m for the molecular layer and 0.15 ± 0.03 S/m for the granular layer) (Okada et al., 1994). The ratio $\sigma_{emolecular}/\sigma_{egranular}$, however, is small enough to be ignored for the present analysis since the ratio $B_{secondary}/B_{primary}$ is ~10% for this ratio (1.67) (Fig. 7, Huang et al., 1990). The conductivity in the hippocampus (CA1 and CA3) is homogeneous across the stratum radiatum and pyramidale based on the measurements carried out by McBain et al. (1990). [The conductivity is given by $\sigma_{saline}\alpha / \lambda_e^2$, where α is the extracellular volume fraction and λ_e is the tortuosity of the extracellular microenvironment (Gardner-Medwin, 1980). The hippocampus is electrically homogenous based on the measured values of α and λ_e (McBain et al., 1990).] The conductivity in the rat barrel column differs across layers but the variation is within 10% of each other (Goto et al., 2010). The conductivity in the monkey primary visual cortex is homogeneous (Logothetis et al., 2007). Thus, these tissues are homogeneous along the depth for our present purpose.

Theoretical study of basis of the apparent empirical invariance in $q_{primary}$

Summary of the cortical network model

The analysis was carried out using an empirically validated mathematical model of neuronal networks (Murakami et al., 2002, 2003). In this model, which is based on the model of Traub and Miles (1991), each pyramidal neuron is represented by a single cylinder with 8 compartments for the basal dendrites, 1 compartment for the soma, and 10 compartments for the apical dendrites. Each cell has six types of voltage