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Estimating cortical column sensory networks in rodents from micro-electrocorticograph (μECoG) recordings

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ABSTRACT

Micro-electrocorticograph (μECoG) arrays offer the flexibility to record local field potentials (LFPs) from the surface of the cortex, using high density electrodes that are sub-mm in diameter. Research to date has not provided conclusive evidence for the underlying signal generation of μECoG recorded LFPs, or if μECoG arrays can capture network activity from the cortex. We studied the pervading view of the LFP signal by exploring the spatial scale at which the LFP can be considered elemental. We investigated the underlying signal generation and ability to capture functional networks by implanting, μECoG arrays to record sensory-evoked potentials in four rats. The organization of the sensory cortex was studied by analyzing the sensory-evoked potentials with two distinct modeling techniques: (1) The volume conduction model, that models the electrode LFPs with an electrostatic representation, generated by a single cortical generator, and (2) the dynamic causal model (DCM), that models the electrode LFPs with a network model, whose activity is generated by multiple interacting cortical sources. The volume conduction approach modeled activity from electrodes separated < 1000 μm, with reasonable accuracy but a network model like DCM was required to accurately capture activity > 1500 μm. The extrinsic network component in DCM was determined to be essential for accurate modeling of observed potentials. These results all point to the presence of a sensory network, and that μECoG arrays are able to capture network activity in the neocortex. The estimated DCM network models the functional organization of the cortex, as signal generators for the μECoG recorded LFPs, and provides hypothesis-testing tools to explore the brain.

1. Introduction

Technological developments in electrophysiology have given neuroscientists the freedom to investigate the brain from new perspectives. Scalp electroencephalography (EEG) has been used to noninvasively record electrical activity throughout the cortex, facilitating the investigation of frequency components recorded globally; however, EEG is limited in spatial resolution (Nunez and Srinivasan, 2006; Niedermeyer and da Silva, 2005). Penetrating electrodes can record spiking activity from individual neurons (Nicolelis et al., 1995; O'Keefe and Dostrovsky, 1971) or local field potentials (LFPs) from a small population of neurons located within a few hundred μm radius (Mitzdorf, 1985; Katzner et al., 2009; Lindén et al., 2011). Intracortical recordings offer precision, specificity, and have been well studied in animals. However, the invasive nature of this technology raises a number of unresolved issues, including reliability, safety, and biocompatibility (Nicolelis and Lebedev, 2009). Electrocorticographic (ECoG) arrays, also known as intracranial EEG, record LFPs with higher spatial resolution and signal-to-noise ratio (SNR) than scalp EEG (Crone et al., 1998; Leuthardt et al., 2004). In addition, ECoG arrays record potentials with less cortical damage and less signal variability than intracortical recordings. MicroECoG (μECoG) arrays are ECoG arrays fabricated at a smaller scale, which decreases the craniotomy size required for insertion. MicroECoG arrays can record LFPs with higher SNR than ECoG (Viventi et al., 2010), have been reliably and safely implanted for long periods of time (Schendel et al., 2014), and are adaptable to brain computer interface (Thongpang et al., 2011) and

Abbreviations: EEG, electroencephalogram; LFP, local field potentials; ECoG, electrocorticograph; SNR, signal to noise ratio; μECoG, micro-electrocorticograph; NITRO, Neural Interface Technology Research and Optimization; DCM, dynamic causal model; NMM, neural mass model; CMC, canonical microcircuit; TDT, Tucker-Davis Technologies; HPF, high-pass filter; SPM, statistical parametric mapping; SD, standard deviation; SEM, standard error of the mean; ii, inhibitory interneurons; sp, superficial pyramidals; ss, spiny stellate; dp, deep pyramidal; NMSE, normalized mean-square error; LRT, likelihood ratio test; GLRT, generalized likelihood ratio test; P_{FA}, probability of false alarm; VC, volume conduction.

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optogenetic technologies (Richner et al., 2014; Park et al., 2014).

Research to date has not provided conclusive evidence as to the neural activity that generates the LFPs recorded from μECoG arrays. Buzsaki et al. (2012) argued that the principal contribution to LFPs is the synaptic transmembrane current from collective groups of neurons; however, multiple distinct neuronal states can generate identical LFPs. Mapping LFPs back to the corresponding signal generators (or sources[1]) is an inverse problem (Nunez and Srinivasan, 2006; Alifanov, 1974), that is mathematically ill-posed, due to the lack of a one-to-one mapping. Investigators commonly undertake a two-step approach to deal with the ill-posed inverse problem. The first step constitutes solving the forward problem; the forward problem involves correlating global and local events, allowing the investigator to determine the contribution of the synaptic and non-synaptic mechanisms to the global LFPs (Einevoll et al., 2007; Li and Ascoli, 2008). The second step is to then use the estimated relationship between local and global events to gain insight into the local activity; however, the technical means to undertake this second step are still emerging. Buzsaki et al. suggested using experimentally observed temporal patterns to time-lock neuronal activity and generate LFPs from a network model of neurons as a possible way forward. We undertook the second step, by analyzing μECoG LFPs with a network model of neurons, to gain insight into the local micro-architecture of a sensory cortical region.

The underlying signal generation of the μECoG LFPs resides within the neocortex, whose structure has been determined to be comprised of cortical columns, based on neurophysiological studies of local neuronal connectivity (Mountcastle, 1997; Hubel and Wiesel, 1974; Oroquieta et al., 2012). Columnar organization has been established anatomically; however, the disparate definitions of the diameter of a cortical column, shown in Table 1, provide a challenge to determining its functional equivalent (Horton and Adams, 2005; da Costa and Martin, 2010; Bastos et al., 2012).

We set out to investigate the underlying signal generation of μECoG recorded LFPs to determine if μECoG recorded LFPs could capture some of the functional structure of the neocortex. To that end, we recorded sensory evoked LFPs epidurally from the cortical surface, using thin-film bilateral μECoG array technology fabricated at the Neural Interface Technology Research and Optimization (NITRO) lab (Richner et al., 2014). Each μECoG electrode was 200 μm in diameter, while the center-to-center distance between adjacent electrodes was 750 μm. The dimensions of this state-of-the-art μECoG array provides a means to analyze LFPs recorded over a range of distances and spatial resolutions to address the extent of cortical column connectivity.

We analyzed sensory evoked LFPs recorded from μECoG arrays with two distinct computational models: a volume conduction model and a network based model. These computational models use distinct solutions to the forward problem, providing different approaches to gain insight into local activity from global events. The Maxwellian volume conduction model is often used to model potentials from ECoG arrays because of its simplicity and reasonable accuracy in modeling activity in nearby electrodes (Nunez et al., 1997; Towle et al., 1999; Robinson, 2003). The volume conduction model assumes LFPs recorded over the array are produced by a single local cortical generator via electrostatics. The electrode with the highest energy is typically identified as the location for the cortical generator that produces LFPs throughout the array. In contrast, dynamic causal models (DCM) (Friston et al., 2003) and multi-variate auto-regressive models (Chang et al., 2012) are generative network models of neurons, as recommend by Buzsaki et al. (2012), and assume the potentials are generated by multiple interacting sources.

In this manuscript, we compare the single-source volume conduction model with a multiple-interacting-sources DCM-based network model. DCM was developed for EEG and magnetoencephalogram analysis and uses cortical-column-inspired neural mass models (NMMs) to estimate connectivity between modeled sources and predict LFPs in the populations[2] and electrodes (David et al., 2006). NMMs are appropriate for sensory evoked LFPs, since the stimulus is modeled to innervate the spiny stellate population of a specified region, and the cortical circuitry responds with large synchronous spatiotemporal patterns. Bastos et al. (2012, 2015). established a relationship between local and global activity, rooted in neurophysiological evidence, to develop the canonical microcircuit (CMC) for DCM. They analyzed ECoG potentials over the visual cortex in non-human primates, scaling DCM down to ECoG dimensions, with regions located 6–12 mm apart. The CMC incorporates an additional pyramidal population for each source, providing a necessary vertical dimension to model μECoG potentials. We employ the CMC in DCM for our network model analysis.

We explored the connectivity and signal generation of cortical sources by comparing the performance of a single-source volume conduction model to a multiple-interacting-sources DCM-based network model in predicting LFPs recorded from a μECoG array with electrodes located at distances that range 750–3000 μm apart. We investigated the spatial dimensions over which the volume conduction model and DCM accurately predict the recorded electrical potentials. We developed DCM-shotgun, a method that increases the likelihood of converging to a model with high fidelity and can be generalized to analyze other datasets generated from animal brain recordings. We compared the performance of a fully connected DCM to an unconnected DCM version to assess the relevance of the extrinsic network component. We implemented bootstrap methods to assess the stability of the parameters of a sensory network estimated by DCM.

We found that activity from electrodes separated < 1000 μm can be described by the single source volume conduction model with reasonable accuracy, but that electrode separations greater than 1500 μm require a network model, like DCM, to accurately predict the potentials observed. We also found that DCM's extrinsic network is the key component in modeling the potentials over the entire array, strongly suggesting the presence of a network of cortical sources independently interacting. Finally, the sensory network for two cortical sources was estimated with DCM to illustrate the local organization of the sensory cortex and provide likely signal generators responsible for the LFPs recorded from the μECoG array.

This paper is organized as follows. Section 2 describes the data acquisition and preprocessing methods, defines the volume conduction model and the DCM, and presents the objective metrics used for assessing the models. Section 3 presents model performance as a function of electrode separation, identifies the relevance of the network component in DCM, and illustrates the estimated sensory network between two cortical sources. Section 4 discusses the relevance and interpretation of the results. Brief concluding remarks are given in section 5. Notation used throughout the paper is introduced here. Boldface symbols represent vectors, while superscript T denotes vector transpose. Given data $\mathbf{v}$, the sample mean is written as $\bar{v}$ and model estimate as $\hat{v}$. $\mathbb{E}[a]$ denotes the expectation of a random variable a. $\mathbf{x} \sim \mathcal{N}(\mu, \Sigma)$ means the vector $\mathbf{x}$ is normally distributed with mean μ and covariance Σ.

2. Materials and methods

2.1. Experimental setup

We recorded sensory evoked potentials using μECoG arrays in four rats, with the following experimental procedure, illustrated in Fig. 1. For each rat, we fabricated a platinum μECoG array with the following specifications: 4 $\times$ 4 grid, 200 μm site diameter, 750 μm site-to-site spacing, and 50 kOhms nominal impedance at 1 kHz (Thongpang et al., 2011). We then implanted bilateral μECoG arrays in each rat, under

[1] Generators and sources are used interchangeably throughout.

[2] Populations refer to a particular type of cell populations.