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Surface-based mixed effects multilevel analysis of grouped human electrocorticography

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ABSTRACT

Electrocorticography (ECoG) in humans yields data with unmatched spatio-temporal resolution that provides novel insights into cognitive operations. However, the broader application of ECoG has been confounded by difficulties in accurately depicting individual data and performing statistically valid population-level analyses. To overcome these limitations, we developed methods for accurately registering ECoG data to individual cortical topology. We integrated this technique with surface-based co-registration and a mixed-effects multilevel analysis (MEMA) to control for variable cortical surface anatomy and sparse coverage across patients, as well as intra- and inter-subject variability. We applied this surface-based MEMA (SB-MEMA) technique to a face-recognition task dataset (n = 22). Compared against existing techniques, SB-MEMA yielded results much more consistent with individual data and with meta-analyses of face-specific activation studies. We anticipate that SB-MEMA will greatly expand the role of ECoG in studies of human cognition, and will enable the generation of population-level brain activity maps and accurate multimodal comparisons.

Introduction

Intracranial EEG (icEEG) recordings are a frequent part of the evaluation of pharmaco-resistant epilepsy at specialized centers. In the United States, there are about a million patients with epilepsy who are likely surgical candidates. icEEG is commonly carried out using subdural grid electrodes (SDEs), yielding summed local neuronal activity around each electrode — termed electrocorticography (ECoG) (Tandon, 2008). In order to precisely delineate the epileptogenic network, SDEs are implanted over both pathologic and functionally normal cortical tissue. While abnormal ECoG is used to make clinical decisions regarding the resection of brain regions, ECoG recordings of local cortical network processes over uninvolved brain areas in these patients can provide multi-lobar, high spatio-temporal resolution sampling from disseminated brain regions (Chang et al., 2011; Sahin et al., 2009; Watrous et al., 2013). These data provide an optimal convergence of coverage and fidelity compared to the spatially limited sampling of microelectrodes (Rutishauser et al., 2011), the poor temporal resolution of fMRI, and the poor signal qualities of scalp EEG (Jerbi et al., 2009; Lachaux et al., 2003).

Cognitive operations are reflected precisely by ECoG recordings of event related broadband activity in the mid-to-high gamma frequency range (60–200 Hz) (Cervenka et al., 2011; Crone et al., 2001, 2006; Gaillard et al., 2006; Lachaux et al., 2003; Ojemann et al., 2013). This gamma-band activity is thought to bind remote regions during cognitive processes (Buzsaki and Draguhn, 2004) such as episodic memory retrieval (Watrous et al., 2013), semantic decoding and confrontation naming (Conner et al., 2011, 2013). Gamma-band activity also robustly correlates with the blood oxygen level dependent (BOLD) signal commonly used to provide insight into similar cognitive processes using functional MRI techniques (Conner et al., 2011; Hermes et al., 2011; Khursheed et al., 2011; Lachaux et al., 2007; Logothetis and Pfeuffer, 2004; Nir et al., 2007; Ojemann et al., 2010). The comparison of ECoG with the BOLD signal (Conner et al., 2011; Esposito et al., 2012; Mukamel et al., 2005) in patients with intracranial electrodes additionally offers an opportunity to elucidate the relationship between hemodynamic and electrophysiological signals, during cognitive processes that cannot be replicated in animal models (Logothetis et al., 2001).

Despite its remarkable properties, the broader application of ECoG to cognitive neuroscience has been limited by three significant disadvantages: 1) Concerns that data collected from epileptic subjects may not reflect normal cognitive function. 2) Electrode coverage in each subject is variable and sparse (*i.e.* limited) due to the fact that clinical criteria dictate electrode placement. 3) The relative scarcity of such data that

Abbreviations: SB MEMA, surface-based mixed effects multilevel analysis; (s/v)-ERZ, (surface/volumetric) electrode recording zone.

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minimizes the potential for broad application to the study of human cognition (Lachaux et al., 2003).

Concerns about the applicability of these recordings to "normal" human cognition have been addressed by patient inclusion criteria based on pre-operative neuropsychological evaluation (*e.g.* IQ > 80), the use of non-complex paradigms that optimize the likelihood of response parameters overlapping with those seen in healthy volunteers, and the inclusion of only those ECoG data that are free of electrophysiological abnormalities (Crone et al., 2006; Halgren et al., 1998; Jerbi et al., 2009; Lachaux et al., 2003). We have previously compared patient fMRI and ECoG recordings against fMRI obtained in healthy volunteers, under identical task conditions, further validating the reliability of such recordings (Conner et al., 2013). This work specifically seeks to address the sparse sampling problem.

To develop icEEG for the generation of broad-field, high-resolution brain activity maps, as well as to contribute meaningfully to multimodal comparisons, the field urgently needs novel methods for individual data representation and grouped analyses (Alivisatos et al., 2013; Pieters et al., 2013). Challenges for individual data representation arise, in large part, as a result of the convoluted geometry of the brain surface. Intracranial electrodes sample discrete patches of cortex related to the type of electrode used — in the case of SDEs this is the crown of the gyrus. Existing techniques for mapping ECoG activity onto cortical models, both volumetric (Conner et al., 2013; Miller et al., 2007) and surface-based (Dykstra et al., 2012; Esposito et al., 2012), have been unable to fully address difficulties in the spatial transformation of electrode coordinates and ECoG activity onto the complex folding patterns of the surface. These include errors introduced during localization of electrodes situated over sulci, and failures to account for local topology when utilizing isotropic Euclidean distance measures for spatial smoothing of ECoG activity. These errors undermine icEEG's high spatial resolution and confound interpretations through the spatial aliasing of activity across functionally distinct regions.

A bigger problem arises with respect to inter-subject comparisons. Individual effect sizes measured by SDEs are robust, but single-subject recordings cannot capture all cortical regions involved in a particular task. Due to the discrete nature of the recordings, ECoG activity will likely underestimate functional representation at the individual level. Circumventing the sparse sampling problem requires combining data across large numbers of subjects to achieve widespread coverage. In this manner, continuous maps of functional activation can be generated that provide a more comprehensive view of underlying cortical networks (Jerbi et al., 2009). Differences in cortical surface anatomy across subjects complicate grouped analyses due to poor alignment of functionally homologous brain regions (Anticevic et al., 2008; Dykstra et al., 2012; Esposito et al., 2012; Oosterhof et al., 2011; Saad and Reynolds, 2012). Errors of inter-subject co-registration render grouped ECoG data imprecise, or worse, inaccurate. Recently, however, advances have introduced the use of surface-based normalization (Fischl et al., 1999b) with ECoG datasets (Dykstra et al., 2012; Esposito et al., 2012; Groppe et al., 2013; Mukamel et al., 2014). This approach offers a practical and computationally efficient method to correct for anatomical variability across subjects (Anticevic et al., 2008; Fischl et al., 1999b; Saad and Reynolds, 2012).

At the group-level, the application of traditional statistical models to neuroimaging datasets has recently been called into question (Chen et al., 2011; Conner et al., 2013; Woolrich, 2008). Conventional group analysis strategies operate on the assumption of negligible, or equivalent, intra-subject variance. Additionally, effect-estimates are assumed to follow Gaussian distributions, without outliers. ECoG data frequently violate these two assumptions, the consequences of which are exacerbated by small sample sizes. Furthermore, conventional grouped-analysis strategies are not equipped to handle missing data from subjects with unsampled cortical regions (Chen et al., 2011; Conner et al., 2013). Given the sparse nature of icEEG, even after combining data across many subjects, much of the cortex remains unsampled (Halgren et al., 1998). Failure to correct for large-scale missing data will distort group effect estimates and inflate statistics (Chen et al., 2011). Thus the analysis of grouped ECoG data requires a multi-level approach that is capable of incorporating individual subject effect sizes and their variances, correcting for missing data, and modeling outliers (Chen et al., 2011; Woolrich, 2008). Such comprehensive statistical approaches have been largely lacking in icEEG literature (Burke et al., 2013; Davidesco et al., 2013; Esposito et al., 2012; Groppe et al., 2013; Khursheed et al., 2011; Kojima et al., 2013; Miller et al., 2007; Vidal et al., 2010; Watrous et al., 2013).

To overcome these limitations, we have developed a pipeline for the topologically accurate and statistically robust surface-based analysis of individual and population-level ECoG data. We developed novel methods to accurately represent recording electrode coverage sites and to depict high frequency ECoG activity on cortical surface models. We integrated these methods with surface-based co-registration to correct for variability in cortical anatomy across subjects, and have adopted a mixed-effects multilevel grouped analytic approach ($n = 22$) to control for sparse sampling and outlier inferences, as well as intra- and inter-subject variability.

We extend prior work in this field in three ways: 1) the spatial transformation of individual SDE coverage to their cortical surface model incorporates the full diameter of each electrode. This preserves the true spatial resolution of the recording electrode, and avoids errors that occur when localizing SDEs situated over sulci with existing coordinate-to-nearest node approaches (Conner et al., 2013; Dalal et al., 2008; Dykstra et al., 2012; Esposito et al., 2012; Hermes et al., 2010). 2) The incorporation of local gyral and sulcal folding patterns during the spatial transformation of subject SDE coverage to the surface. By modeling underlying cortical geometry at each electrode, this approach prevents erroneous assignment of activity to neighboring cortical regions, which may be closely situated in Euclidean space but are in fact functionally distinct structures (*e.g.* opposing banks of a sulcus) (Anticevic et al., 2008; Fischl et al., 1999b; Weiner and Grill-Spector, 2013). 3) The adaptation of a mixed-effects multilevel analysis (MEMA) approach that avoids assumptions of equivalent or negligible intra-subject variability, corrects for missing data, and is capable of modeling outliers. Compared to conventional statistical models, the MEMA approach yields increased statistical power, more accurate grouped effect-estimates, and is better equipped to handle ECoG data (Chen et al., 2011; Conner et al., 2013). We validated our pipeline using data collected during a famous face-naming task and comparing our results against current methods of individual and grouped ECoG analysis.

Methods

22 patients (13 female, mean age 35 ± 11 years, mean IQ 99.5 ± 8.5), scheduled for SDE implantation (14 LH, 5 RH, 3 bilateral), were enrolled with informed consent. A total of 2518 (1799 LH, 719 RH) individual subdural electrodes were implanted (PMT Corporation; 4.5 mm diameter, 3 mm diameter contact with cortex) using standard neurosurgical techniques (Tandon, 2008). Of these, we excluded 391 (286 LH, 105 RH) due to proximity to sites of seizure onset, inter-ictal spikes, or 60 Hz noise; the remaining 2199 SDEs were analyzed.

Cortical surface models and electrode localization

Cortical surface models were reconstructed from subject pre-implantation anatomical MRI scans (Phillips Medical; T1-weighted, 1 mm isotropic resolution) using FreeSurfer software (v5.1) (Dale et al., 1999), and then imported to the SUMA module of AFNI (Cox, 1996). SDEs were localized using intra-operative photographs combined with a recursive grid partitioning technique, and spheroids were generated to model the SDE location on the cortical surface model (Pieters et al., 2013).