Published in final edited form as:

Epilepsy Behav. 2013 November ; 29(2): 259–268. doi:10.1016/j.yebeh.2013.08.012.

Proceedings of the Fourth International Workshop on Advances in Electroconvicography

Anthony Ritaccio^a, Peter Brunner^{a,b}, Nathan E. Crone^c, Aysegul Gunduz^d, Lawrence J. Hirsch^e, Nancy Kanwisher^f, Brian Litt^g, Kai Miller^h, Daniel Moranⁱ, Josef Parvizi^h, Nick Ramsey^j, Thomas J. Richner^k, Niton Tandon^l, Justin Williams^k, and Gerwin Schalk^{a,b}

^a Albany Medical College, Albany, NY, USA ^b Wadsworth Center, New York State Department of Health, Albany, NY, USA ^c Johns Hopkins University School of Medicine, Baltimore, MD, USA ^d University of Florida, Gainesville, FL, USA ^e Yale University School of Medicine, New Haven, CT, USA ^f McGovern Institute for Brain Research at MIT, Cambridge, MA, USA ^g University of Pennsylvania, Pittsburgh, PA, USA ^h Stanford University, Stanford, CA, USA ⁱ Washington University, St. Louis, MO, USA ^j University Medical Center, Utrecht University, Utrecht, The Netherlands ^k University of Wisconsin-Madison, Madison, WI, USA ^l University of Texas Health Science Center, Houston, TX, USA

Abstract

The Fourth International Workshop on Advances in Electroconvicography (ECoG) convened in New Orleans, LA, on October 11-12, 2012. The proceedings of the workshop serves as an accurate record of the most contemporary clinical and experimental work on brain surface recording and represents the insights of a unique multidisciplinary ensemble of expert clinicians and scientists. Presentations covered a broad range of topics, including innovations in passive functional mapping, increased understanding of pathologic high-frequency oscillations, evolving sensor technologies, a human trial of ECoG-driven brain-machine interface, as well as fresh insights into brain electrical stimulation.

Keywords

electroconvicography; brain-computer interface; high-frequency oscillations; brain mapping; seizure detection; gamma-frequency electroencephalography; neuroprosthetics; subdural grid

1. Introduction

The Fourth International Workshop on Advances in Electroconvicography (ECoG) convened in New Orleans, Louisiana, in October 2012. Once again, the rapidly expanding repertoire of ECoG-based clinical and investigational roles was explicated by an international faculty of the most prolific experts in the field. Our bold keynote address by Prof. Nancy Kanwisher set the tone by extolling the virtues of ECoG in elucidating temporal causation and

© 2013 Elsevier Inc. All rights reserved.

Corresponding author: Anthony Ritaccio, MD, FAAN, FANA Department of Neurology Albany Medical College Albany, NY, USA RitaccA@mail.amc.edu Tel: (518) 262-0554 Fax: (518) 262-6261.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

connectivity unsettled by functional MRI and diffusion tractography. This theme was dominant throughout both days of the workshop and across the represented clinical, engineering, and neuroscience domains as established and novel ECoG applications were illuminated (Table 1). The proceedings of our gathering follow.

2. Keynote Address: Domain-Specific and Domain-general Components of Mind and Brain

Functional magnetic resonance imaging (fMRI) research over the last 20 years has discovered a number of brain regions that are remarkably specific in the perceptual/cognitive operations they carry out (e.g., face recognition, understanding other minds, and sentence understanding). Each of these regions is present in approximately the same location in essentially every normal brain; these regions are fundamental components of the human mind and brain.

Despite this important progress, three fundamental questions remain. First, what is the causal role of each of these regions in perception and cognition? Functional MRI cannot answer this question; it is necessary to intervene on a system to test its causal role. Second, what is the time course of engagement of each of these regions? fMRI has very low time resolution, hence confounding bottom-up processing with subsequent interareal interactions and feedback occurring hundreds of milliseconds to seconds later. Third, what is the structural connectivity of these regions? Diffusion tractography suffers from notorious ambiguities, and analyses of correlations in the time course of the blood oxygen level-dependent (BOLD) response have focused on temporal fluctuations that are very slow and unlikely to represent the full pattern of connectivity in the brain. I argue that intracranial recording and stimulation offer the most promising prospect yet of overcoming the inherent limitations of fMRI to make real progress in understanding the causal role, time course, and connectivity of brain regions that have been richly characterized by fMRI.

3. Basic ECoG Physiology

3.1 A Useful Adjunct in Understanding the ECoG Signal: Spectral Motifs

When examining the ECoG signal, a common approach is to isolate power spectral densities (PSDs) of the electric potential and divide them into “bands.” Each of these bands is typically analyzed independently, and different frequency ranges are often ascribed distinct physiological interpretations (i.e., the theta, alpha, beta, or gamma band). In some cases, however, the power at each frequency may represent a superposition of underlying spectral motifs which each represent different electrophysiological phenomena.

While there are many potential ways to uncover and characterize these spectral motifs, one way that has been used is an orthogonal decomposition in frequency space. Consider, for example, the PSD measurement from a thumb-specific precentral site during movement of the thumb or the fingers, and during rest, illustrated in Fig. 1B (subject 5 from Miller et al. [1]). There is a decrease in the amplitude of low-frequency power and a broadband increase in power above a “junction” in the PSD at ~35-40 Hz [2]. A common approach to understand power spectral changes would be to assign a low-frequency band (LFB: 8-32 Hz) to capture this decrease and a high-frequency band (HFB: 76-100 Hz) to capture the increase [3]. As shown in Fig. 1C, one can plot the movement and rest power in a 2-dimensional HFB-LFB feature space. Naive rotation of the data in this feature space using a principle component type of decomposition more plainly isolates thumb movement from other finger movements, as well as rest (1st principle spectral component, PSC), and perhaps represents the data in a space that more directly reflects the underlying physiology.

This concept can be extended beyond two 25-Hz bands and applied to a high-dimensional space where each dimension is the power at each Hz. The shape of the resulting PSCs may yield insight into the types of electrophysiological phenomena from which the PSDs are built. For the example in Fig. 1D, the first PSC, which robustly distinguishes thumb movement from rest, is flat across frequencies. This flat shape, extracted from log SD, indicates a multiplicative factor that is constant for all frequencies. Because this background shape has been shown to follow $P \sim 1/f^\alpha$, which is conserved during movement, this first PSC can be linked to increases and decreases in a stochastic process [4]. The second PSC is peaked at a particular frequency and reflects increases and decreases in the alpha/beta motor rhythm [1], whereas the third PSC is peaked in the theta range [5]. The PSD can be reconstructed from subsets of the PSCs to reveal these stochastic and rhythmic components more plainly (Fig. 1E&F).

This type of decomposition has also been used to generate more natural feature set for classification of words in a microelectrocorticographic recording during language production [6] and also to generate improved features for identification of motor imagery states in EEG [7]. Onton and Makeig [8] showed that similar PSD decompositions, using independent component analysis, were able to uncover unique motifs that could discriminate cognitive states from EEG measurement. We recommend that spectral decomposition be tried as an adjunct to classic frequency-band approaches both to increase understanding of the underlying signal and to generate more robust spectral features for classification.

3.2 Basics of ECoG Signal Acquisition

Over the past 60 years, the use of ECoG in the presurgical evaluation of epilepsy has proliferated from its initial application at the Montreal Neurological Institute to widespread use around the world. Over the past two decades, it has become increasingly clear that, in addition to its important role in presurgical evaluation, ECoG also provides a unique window into human brain function [10-12].

Despite the resulting increasing interest in ECoG, the sensor technology has remained effectively unchanged. For example, the electrodes that are commonly used for clinical purposes are connected to an external biosignal amplifier through individual wires. Because these wires require an opening in the skull and skin and thus tether the subject to its environment, it is impracticable to implant a large number of electrodes. While this limitation does not substantially affect presurgical evaluation of epilepsy, which depends on time-consuming electrical stimulation of the brain, it has set distinct limits for our ability to study brain function at increasing spatial detail and coverage.

Recent efforts have begun to change this situation with the advent of biocompatible thin film sensors that can be manufactured cost-effectively to accommodate hundreds of electrodes [13]. The most advanced versions of these sensors can also incorporate flexible electronics to amplify and digitize the ECoG signals close to the source [14]. This allows for high spatial resolution (e.g., 1 mm) and wide cortical coverage. With the requisite approvals, this technology will create entirely new opportunities for studying the human brain.

In addition to necessary improvements of the sensor, it has become increasingly clear that current processing methods do not take optimal advantage of the resolution and signal-to-noise ratio of ECoG signals. While it is widely known that there is substantial variability in ECoG signals across trials and across individuals, and while it has become increasingly clear that important aspects of behavior are represented by complex brain signal processes rather than individual brain signal features, current processing methods typically average across trials or individuals and usually only assess the statistical properties of individual brain signal features. These limitations of existing processing/statistical techniques are

unfortunate, because more complex procedures that can extract complex signal features and put them in relationship with each other have led to important new discoveries in other areas of research, such as computer vision. This approach requires advanced processing, machine learning, and statistical methods, as well as the ability to acquire and combine physiological (e.g., ECoG) with behavioral (e.g., eye-gaze, motion) and nonphysiological (e.g., electrical cortical stimulation, ECS) imaging. The efforts to establish these techniques and to apply them to neuroscientific study of ECoG have just begun.

The ongoing improvements in sensor and processing technologies have important implications not only for the continual advancement of our understanding of the human brain but also for an entirely new range of clinical applications that support the automated detection, localization, and intervention of cortical dysfunction and the mapping and interaction with distributed cortical function.

3.3 Basics of ECoG signal analysis

The last decade has seen an immense rise of interest in the decoding of brain states as measured through ECoG, due to the fine spatial and temporal resolution and high fidelity these signals offer. Signal analysis techniques provide the means to extract task-relevant ECoG features from background neural activity and have been instrumental in advancing our understanding of cortical rhythms and asynchronous local activity of the human brain. This section introduces the basics of ECoG signal analysis. Interested readers can find comprehensive reviews on electrophysiological signal analysis and modeling in the literature [15-17].

Analysis of ECoG signals can start during recording, with the visual inspection of incoming channels. Most data acquisition software will allow for visual filtering of signals, such as de-meaning for removal of DC components, high-pass filtering for drift removal, and notch filtering for line noise removal, all of which can be replicated offline. Artifacts isolated to single or few channels due to bad contact with cortical surface or to ictal or interictal activity should be omitted from further analyses. Artifacts common across channels can be removed by applying spatial filters. The most commonly used spatial filters are common average reference (CAR) and Laplacian filtering [3]. A CAR filter removes the spatial mean of all channels from the raw time series of each channel. Laplacian filters compute spatial means more locally, within the 4 or 8 neighbors of a channel. This neighborhood mean is then subtracted from the channel, and the process is repeated for each channel.

Characterization of neural correlates of behavior using ECoG relies on isolating its spectral subcomponents, mainly the rhythmic oscillations (which appear as peaks in power spectra and are spatially broad) and asynchronous local activity (which appears as spatially localized broadband modulations over spectral ranges greater than 70 Hz) [3]. Spectral estimation can be performed by means of band power computations at filter-bank outputs, fast Fourier transform (FFT), or autoregressive (AR) modeling [17]. Band power computation is fairly straightforward and requires a simple filter design for the frequency band of interest. However, it is not practical during the exploratory stages of data analysis when the frequency ranges of interest are unknown and multiband tracking is essential. The fast Fourier transform converts the time series ECoG signal into the frequency domain where its magnitude reveals the spectral content of the signal. Autoregressive modeling can provide higher spectral resolution compared to the fast Fourier transform. However, it is a parametric model in which the accuracy of the spectral estimate relies on the model order selected by the investigator. McFarland et al. [18] discuss optimal AR model order selection.

ECoG spectral features that are task relevant can be identified by contrasting the spectra computed during behavioral/cognitive engagement with baseline spectra. The r^2 measure,

also known as the coefficient of determination, provides a statistical comparison metric of how strongly the means of the spectral features for the two task conditions differ in relation to the variance of the data [17]. High r^2 values suggest that the channel and spectral range at hand significantly modulate during the task. This in turn suggests that behavioral engagement may be inferred from ECoG signals.

4. Clinical ECoG Domains

4.1 Electrocorticography: Clinical Primer

Intracranial electroencephalogram (EEG) recordings are indicated for surgical treatment of refractory epilepsy when other tests to identify the seizure focus are discordant or inconclusive, when there is no MRI abnormality (except select medial temporal cases), when the seizure onset zone abuts eloquent cortex (including many lesional cases), with dual pathology (e.g., hippocampal sclerosis plus a lesion), and occasionally in other scenarios. Although some cortical mapping and identification of the irritative (“spiking”) zone can be done via intraoperative ECoG, implanted electrodes are usually required to identify the seizure onset zone. Complete removal of the seizure onset zone is associated with a greater chance of seizure freedom, even after accounting for lesion resection [19].

There is no good evidence that intraoperative ECoG can help guide neocortical resection during temporal lobectomy in patients with mesial temporal sclerosis; one study suggested that it may be beneficial in guiding the posterior extent of hippocampal resection. Intraoperative ECoG may be adequate to guide resection in select cases with focal cortical dysplasia if continuous spiking is seen, as occurs in about two-thirds of cases [20]. There is no proven use for activation techniques, determination of afterdischarge thresholds, or elicitation of habitual auras/seizures in surgical planning--and some evidence that all of these can be misleading.

Complications of implanted intracranial electrodes are fewer than 10% and mostly transient, with permanent deficits in <1-2% and rare mortality [21]. Risks are higher with greater numbers of implanted electrodes, larger subdural grids, and peri-Rolandic location. The relative utility of subdural strips/grids, depth electrodes, stereo-EEG, and combinations of these are unknown. Recent gamma activation mapping techniques may speed up functional mapping, including determination of broad language networks, either intra- or extraoperatively [22].

Mesial temporal onset seizures on depth electrode recordings often begin with rhythmic spiking at <2 Hz or low-voltage 10-16 Hz activity. Unfortunately, spread to the hippocampus can look identical. Well-localized neocortical onsets often start with low-amplitude fast activity, typically >16 Hz, often >30 Hz. Many seizure onsets are difficult to localize to a discrete area and may involve wider epileptogenic networks, such as the medial temporal/limbic network, the medial occipital/lateral temporal network, and the superior parietal/medial frontal network [23].

High-frequency oscillations (HFOs; ripples: 80-250 Hz, and fast ripples: 250-600 Hz) may help localize epileptogenic tissue [24,25]. Fast ripples seem to be more specific than ripples for seizure onset zones, especially when associated with interictal spikes [26]. HFOs may be more localizing than traditional interictal epileptiform discharges [24,25]. Identification of HFOs requires high sampling rates (preferably at least 2,000 Hz) and different filter and “paper speed” settings. One small recent study suggested that single-pulse stimulation-induced fast ripples were suggestive of the epileptogenic zone [27]. Devices are now available for recording chronic ambulatory intracranial EEG, although only in research trials to date. Such devices may allow seizure prediction and warning, which would improve

patient safety and quality of life, as well as allow responsive treatment for seizure prevention (e.g., via stimulation, cooling, or medications). Electrographic signal analysis is also useful for brain-computer interfaces (see Section 5).

4.2 Functional Mapping Using Electrical Stimulation

Electrical brain stimulation (EBS) consists of delivering electrical pulses to a given region of the brain, sometimes in a deep subcortical nucleus such as subthalamic nuclei, in which case the procedure is traditionally known as deep brain stimulation (DBS). Others have also used the term direct cortical stimulation (DCS) for electrical charge delivery in a cortical region. A problem with these terms is that they were coined at a time when the mechanism of action of electrical charge delivery to the brain was thought to be a pure excitation of the targeted area. This is no longer the case. Although we still do not know how electrical charge delivered to a multilayered cortical structure behaves, we have reason to believe from subcortical studies that the delivered electrical buzz (depending on its frequency) modulates or perturbs the function of the cellular circuitry and its connections [28].

Bipolar currents (as low as 10 mA) delivered between two adjacent electrodes might affect several thousands of pyramidal cells [29] whose axons are more excitable than their cell bodies [30]. Moreover, there is evidence that the electrical charge is taken up by the afferent and efferent axons, and thus the electricity propagates anti- and orthodromically to wherever these fibers are connected [31,32]. Thus a plausible hypothesis is that the electrical charge delivery in a cortical or subcortical site leads to modulation of the function of the targeted neurons as well as the interconnected anatomic structures. For instance, electrical stimulation of V1 is known to change the activity of neural structures connected with the V1 (e.g., areas V2, V3, and MT) [33].

Since each region of the brain has its selective neuroanatomic connectivity with cortical and subcortical structures, it is reasonable to assume that the effect of EBS may remain “localized” within that specific neuroanatomic network. Although this issue has not been systematically studied, and despite the current critical views about EBS [34], a large body of clinical observations [35] suggests that the perceptual and behavioral effects of the electrical stimulation remains impressively selective (e.g., see selective perceptual changes with cortical [36] and subcortical stimulations [37]). The percept that is generated with stimulation of a target brain region is no longer reproducible with stimulation of the brain tissue a few millimeters away. In this sense, EBS could be seen as electrical modulation of a selective neuroanatomic network, rather than injecting electrical pulses injected to a diffuse brain space.

This interpretation of EBS fits well with the notion of brain functions being distributed in a set of interconnected neural structures, and that EBS alters the function of a distributed, yet anatomically selective, network. Despite the pervasive corticocentrism in modern neurosciences [38], it is possible that some of the higher cognitive changes induced with cortical EBS might be due the propagation of electrical pulses to its subcortical rather than cortical targets.

4.3 Seizure Mechanisms, Microelectrocorticography and Therapies in Epilepsy

The basic principles for nonmedication therapies for epilepsy, particularly surgery and devices, were established by Wilder Penfield and Herbert Jasper in their landmark textbook, *Epilepsy and the Functional Anatomy of the Human Brain*, published first in 1954 [39]. In this text, the authors proposed that there are generators of seizures that can be localized both electrically and according to the clinical symptoms, or “semiology,” associated with these discrete events. Over the past 10 years, there has been a dramatic change in our

understanding of these events, ranging from the identification of high-frequency biomarkers of epileptic networks, ripples, fast ripples, and microseizures [24,40] to functional circuits in brain that can be modulated by implantable devices both open and closed loop [41,42]. Recent studies have looked at these events multiscale, identifying populations of single cells, or units, that are activated [43,44], unchanged, or suppressed as seizures arise, up to the level of chronically implanted standard ECoG electrodes that can be used to forecast seizures with meaningful statistical significance more than 30 minutes prior to seizure onset [45]. These advances are the result of an appreciation that mapping neuronal networks involved in seizure generation will be essential for improving therapy. In addition, they are potent drivers of new technology to make practical multiscale intracranial EEG systems a reality.

Technological advances will be required to exploit our rapidly expanding knowledge of the importance of epileptic microdomains on seizure generation and “epileptogenesis,” the process of making brain epileptic after injury. These technological advances fall into three major categories: high-resolution electrode systems; new machine learning, statistical, and computer science tools to handle and interpret “big data” associated with these systems; and new implantable device technologies to exploit these high-resolution data. Progress has been incremental but steady. New flexible passive and active electrode systems are making high-resolution recording over clinically significant regions—tens of square centimeters of cortical surface—tractable [14]. Cloud-based computing and data sharing platforms, along with unsupervised learning, are taking human bias and variability out of data analysis and making terabytes of data accessible to new algorithms for classification. Finally, creative new implantable devices that telemeter out continuous ECoG and eventually microelectrocorticographic signals, are already recording humans and canines with epilepsy for periods of years [45,46].

These advances, coupled to a growing understanding of neural circuitry from tools such as optogenetics and two-photon microscopy, are rapidly generating more data and possibilities to find new surgical and device therapies at an impressive rate. The key to leveraging these advances to treat patients will be sharing technological advancements as well as data, algorithms, and techniques among multiple disciplines. The future appears bright for this field, although it will likely require steady encouragement from funding agencies to emphasize teamwork and scientific goals rather than individual accomplishment.

4.4 Application of ECoG Advances

Potential clinical use in preoperative functional mapping has always motivated its development by neurologists and neurosurgeons caring for the patients in whom these recordings are necessary. Although electrocortical stimulation mapping (ESM) is still the de facto gold standard for predicting postresection neurological impairments, ECoG has important practical advantages over ESM that make it attractive in clinical settings [47]. These include the avoidance of seizures and pain triggered by electrical stimulation and the ability to assess the function of all recording electrodes simultaneously, potentially reducing the time needed for comprehensive brain mapping.

Despite these advantages, however, ECoG has not been widely used for clinical purposes. One reason has been a lack of consensus about which components of ECoG signals serve as the best index of task-related cortical activation. Although cognitive neurophysiologists studying human brain function have successfully used phase-locked (e.g., event-related potentials) and non-phase-locked signal components in a variety of frequency bands, most recent studies have focused on task-related power modulations in high gamma (~60–200 Hz) frequencies [48].

Perhaps the most important reason why ECoG has not been adopted for clinical use is the level of technical difficulty and the lack of immediacy in its implementation. Furthermore, until recently, analyses of task-related ECoG signal changes were performed off-line, after the completion of testing, lacking the immediate feedback to which clinicians are accustomed during ESM. Over the past several years, application of brain-computer interfacing (BCI) techniques to the arena of real-time functional mapping in the clinical domain has proved extremely fruitful in the evolution of a passive real-time ECoG mapping alternative to ESM. Specifically, the group at the Wadsworth Center/Albany Medical College has been developing a novel functional mapping procedure based on a new detection algorithm, called SIGFRIED [49,50], which is incorporated into our general-purpose BCI software, called BCI2000 [51]. Together with appropriate signal acquisition hardware, this procedure interprets, without configuration by an expert and at the patient's bedside, changes in ECoG signals that are passively recorded from electrode grids already implanted in the patient for clinical reasons. Within minutes, this novel method identifies, on a 2- or 3-dimensional topographical display that is updated in real time as the patient performs different tasks, those cortical locations whose activity changes in response to the task (see Fig. 2 for results of our mapping in one patient).

The concept of our real-time functional brain mapping procedure is illustrated in the left panel of Fig. 2. Prior to functional mapping, we acquire postoperative CT scans (A1) and preoperative structural MRI scans (B1). From these scans, we reconstruct the grid position (A2) and cortical surface (B2), which provides a subject-specific anatomic model (D) for our functional mapping technique (E). At the bedside, we engage the subject in different tasks, such as auditory stimulation (C1), which modulates brain signals (C2) in the gamma band (70-110 Hz). BCI2000 software applies the SIGFRIED method to detect these task-related changes and maps the results in real time onto the subject-specific anatomic model (E).

In the right panel of Fig. 2, we present exemplary results from one subject who was implanted over the left hemisphere with 120 electrocorticographic electrodes for the purpose of functional brain mapping and for localizing epileptic foci. Location and duration of the implantation were solely determined by clinical criteria. A lateral X-ray (F) and an operative photograph (G) depict the configuration of two grids and three strips.

In the example shown in H and J, we presented the subject with voice and tone stimuli that induced cortical power changes in the gamma band. To identify brain regions related to receptive language, the software statistically contrasted the brain signal changes induced by tones with those induced by voice stimuli. The 2-dimensional interface to the investigator (H) presented functional activations in real time using a topographical interface that represents the electrode grid. The interface contained a display of cortical activation at each location for each task condition (i.e., voice, tones or language). Each display contained one circle at each electrode's location. The size of each circle and its tint was proportional to the magnitude of cortical activation. The 3-dimensional interface to the investigator (J) presented the same functional information in real time on the patient-specific anatomic model. The results for cortical stimulation (ECS) mapping of receptive language function (F, red) are congruent with those achieved using our passive SIGFRIED-based method (H/J).

Because our procedure rapidly, accurately, and safely maps functional cortex, it has the potential for widespread integration in resective brain surgery protocols and may prove uniquely useful in the pediatric population in which electrical stimulation has numerous operational and physiological barriers. SIGFRIED-based mapping is in active use in several epilepsy surgery programs as an adjunct to conventional ESM methods, serving as a comparator as well as a primer to electrical mapping to enhance efficiency in choosing

“eloquent” sites early in mapping paradigms. The latter has foreshortened time-consuming aspects of ESM in the chronic and operative settings.

To date, together with our collaborators, we have validated the efficacy of our new method for functional mapping in three studies with adult and pediatric patients [22] at the bedside and in intraoperative scenarios [52]. We also showcased our method in several relevant conferences and in four dedicated workshops on ECoG organized by our group. Finally, we provided our prototype to several clinics in the USA and in Europe, and licensed the technology to a corporate partner. The initial version of the resulting product is being rolled out to clinical testing (cortIQ/g.tec medical engineering).

5. Integration of ECoG Research

5.1 Grouped Analysis and Multimodal Comparisons of ECoG Data

Electrocorticography yields neural recordings of unparalleled spatiotemporal resolution that can provide novel insights into human cognition [53-55]. These characteristics of ECoG allow for intermodal comparisons and for evaluating functional cerebral connectivity [56]. Yet, for ECoG to contribute meaningfully to the generation of broad-field, high-resolution brain activity maps, novel tools are needed for individual data representation and grouped analyses [57].

Using three-dimensional mesh models to describe cortical surfaces, and intraoperative photographs, we are able to represent subdural electrodes (SDEs) precisely on individual cortical surfaces. A recursive grid partitioning technique [58] allows for rapid localization and display of SDEs. Additionally, parcellation of the cortical surface allows for anatomic labeling of the recording sites and facilitates grouped comparisons. Implantation of SDEs is dictated by clinical considerations; coverage is sparse and variable across individuals. To circumvent the sparse sampling problem, we used large sample sizes and developed a statistically robust analytic technique called mixed effects meta-analysis (MEMA) to correct for variations in the effect size of the recorded signal both within and across subjects [55]. We applied this co-registration and analytical method on ECoG data from a group of 19 patients (1,942 SDEs) to examine broadly disseminated cortical networks during retrieval of distinct lexical categories. Both noun and verb generation evoked overlapping, yet distinct nonhierarchical processes favoring ventral and dorsal visual streams, respectively. Notable differences in activity patterns were observed in Broca's area and superior lateral-occipital regions (verb > noun) and in parahippocampal and fusiform cortices (noun > verb) (Fig. 3). Comparisons with fMRI results yielded strong correlation between BOLD signal and gamma power and an independent estimate of group size (>13) needed for fMRI studies of cognition. These findings imply parallel, lexical category-specific processes, reconcile discrepancies between lesional and functional imaging studies, and illustrate the power and utility of grouped ECoG analyses.

Additionally, the ability to precisely co-localize ECoG data with individual anatomy enables comparison with other modalities. Comparing activity measured by ECoG with that measured by fMRI [59-61], we found that power in the mid-gamma band (60-120 Hz) correlates positively and power in the beta band (13-30 Hz) correlates negatively with the BOLD signal. Importantly, the location (i.e., lobe) of the recording site modulates the relationship between ECoG and the observed fMRI response, while the type of language task does not. Across all brain regions, ECoG activity in the gamma and beta bands explains about 22% of the fMRI response, but if the lobar location is considered, 28% of the variance can be explained. This finding carries implications for regional modeling of the hemodynamic response function and may be an essential prelude to inter-regional fMRI comparisons.

We have also made a comparison between diffusion tensor imaging (DTI) tractography and ECoG [62] by developing a processing stream in which fiber tracts near SDEs showing task-related functional responses are isolated to explore structural networks related to working memory maintenance. Such ECoG-constrained tractography may reveal structural connectivity patterns to help better understand the patterns of functional connectivity determined from ECoG.

5.2 Cortical Pattern Decoding of Complex Motor Behaviors

Electrocorticography is one of the tools available for furthering our understanding of human brain function, as is the more widely applicable fMRI technique. Whereas ECoG has superior temporal and spectral information on neuronal activity, it is severely limited in coverage of gray matter. Electrodes measure electrical signal from their immediate vicinity (signal drops off by the square of the distance or more), leaving the tissue between electrodes unseen. Standard clinical grids sample no more than 4% of the surface underneath the grid. Functional MRI, on the other hand, measures from the entire brain, at resolutions as high as 10 mm³ (2-mm isotropic cubes of tissue). The BOLD signal is an indirect measure of neuronal activity since it measures hemodynamic responses to changes in local metabolic demand. The sluggish response (lasting 2-16 s) results in poor temporal resolution and does not distinguish spectral components of the electrophysiological signal. Moreover, the BOLD signal is confounded by vascular properties unrelated to neuronal activity [63-65]. In recent studies, however, we have brought these two functional imaging modalities closer together by using ultra-high magnetic fields (7T and higher) that reduce the vascular artifacts [66] and reveal a tight relationship between electrophysiology and BOLD signal.

We investigated the relationship between ECoG signal and BOLD in the same individuals (epilepsy patients) in terms of signal amplitude and spatial distribution. Using high-density grids (3-mm electrode spacing) on the hand region of the sensorimotor cortex, we measured signal amplitude at increasing rates of hand movement. The fMRI signal, obtained with the same paradigm but before surgical grid implantation and co-registered in space to the grids, saturated at rates higher than 0.5 Hz, as expected [64]. This apparent nonlinearity of the neurovascular coupling is regarded as a feature of the cerebrovascular system and a limitation of the utility of fMRI. Surprisingly, the ECoG signal, notably the power in the 65-95 Hz gamma band, which has been shown to correlate best with BOLD [67,68], was also affected by movement rate: at 1 Hz and higher the amplitude of the gamma response decreased by almost 50% [69]. The apparent deviation from linearity of the BOLD response was explained for almost 80% by the newly found effect of rate on the gamma response [70]. We also examined the spatial pattern of activity associated with movement of separate fingers (thumb, index, little finger). Here we found that finger representation was highly detailed for ECoG (adjacent electrodes responded differently to different fingers) as well as for BOLD. Moreover, with both data sets co-registered, the spatial patterns correlated significantly between modalities (unpublished results). These results indicate that BOLD imaging at 7T yields activation patterns that map surprisingly well onto activity maps obtained from ECoG.

With the close match between ECoG and 7T fMRI, complimentary properties constitute a powerful combination. Human brain function is increasingly viewed as stemming from local and global networks of respectively neuronal ensembles (mm scale) and brain regions (cm scale and up). Of particular interest are the local networks, the full exploration of which has not been possible with the available imaging techniques. Now, with the 7T systems available and the emerging high-density ECoG grids, local networks can be investigated in great detail. Topographical organization can be explored and mapped with 7T in healthy volunteers, and well-placed high-density grids in epilepsy patients can subsequently elucidate the temporal and spectral features of the local networks.

We adopted this approach to investigate sensorimotor representation of hand gestures (sign language) and speech. Both serve communication and are of interest for intracranial brain-computer interface (BCI) decoding for paralyzed people. Functional MRI of gestures and for phoneme generation revealed a well-defined pattern of activity on M1 and S1, with little evidence of different patterns for different signs or phonemes. However, classification of the individual gestures was quite high (>65 % correct, chance level 25%), indicating that the magnitude of activity was significantly and consistently different across the network for each gesture. Classification results were comparable in two patients with ECoG grids (using 65-95 Hz broadband power, >80% correct). Phoneme generation could not be classified well with fMRI (<40% correct, chance level 25%), but with ECoG good classification was achieved by adding temporal features (>70%). These results suggest that decoding of silent speech and attempted sign language for BCI may be feasible. It also shows the advantage of using 7T fMRI to identify candidate brain regions for BCI.

In summary, BOLD imaging at ultra-high field and high-density ECoG yield similar activity patterns in human sensorimotor cortex, at a scale that appears to match the topographical organization. The studies described above suggest that higher density grids may still capture more information, since fMRI displays spatial patterns at a submillimeter scale [71]. The sensorimotor findings bear relevance for the choice of sensors for decoding sign language and silent speech with intracranial BCI.

5.3 Bidirectional Electrocorticographic Brain-Computer Interface

Bidirectional BCIs allow a user not only to control an external device via cortical recordings but also to receive feedback (e.g., sense of touch) via cortical stimulation. Unfortunately, the optimal location for recording a cortical control signal (primary motor cortex) and providing sensory stimulation (primary sensory cortex) are located right next to each other in the brain. Given that typical cortical stimulation levels (volts) are six orders of magnitude larger than cortical recording levels (microvolts), it is very difficult to simultaneously stimulate and record (i.e., concurrent bidirectional BCI) given the large stimulation artifact. One way to deal with this problem is to design a stimulation waveform that has a very different frequency content from the recorded cortical control signal and use filtering techniques to remove the unwanted artifact. Unfortunately, the most effective stimulation patterns have frequency content in the single-unit recording spectrum.

ECoG-based BCIs have an advantage over single-unit-based BCIs in that their signals are an order of magnitude lower in frequency content. By designing and building a custom preamp with a steep (8th order) hardware-based low-pass filter (100 Hz cutoff), we were able to concurrently record high-fidelity microECoG activity over motor cortex while providing a salient and effective percept in primary sensory cortex via electrocortical stimulation. Recently, we trained a monkey using a forced-choice, two-interval task to control a two-dimensional cursor via ECoG-based signals while concurrently receiving electrocortical stimulation that cued the animal to the desired target. The combination of ECoG-based recordings with electrocortical stimulation provides a viable solution to true concurrent bidirectional BCIs.

5.4 The Initial Experience with an Electrocorticographic Brain-Computer Interface in an Individual with Tetraplegia

Studies in able-bodied individuals undergoing presurgical brain mapping [11,72] and studies in nonhuman primates [73,74] have demonstrated successful real-time control of assistive devices using ECoG signals. One question of both clinical and scientific importance is whether ECoG-based BCI control can be achieved in individuals with chronic paralysis; a second question is whether such BCI control can be retained over an extended period of

time. In this study, we recruited an individual with tetraplegia caused by a complete cervical spinal cord injury [75]. The study followed all guidelines of human subject research, and informed consent was obtained before the initiation of any research procedures. A high-density ECoG grid with 32 mesoscale disc electrodes (2 mm in diameter and 4-mm spacing; Fig. 4) was implanted over the left sensorimotor cortex in the study participant for 28 days. We first conducted open-loop motor screening tasks where the subject attempted to perform various hand and arm movements. We observed that cortical representation of arm and hand movement persists despite chronic paralysis and that its spatial, temporal, and spectral patterns closely mimic those that were observed in able-bodied individuals [3,10,76].

The subject achieved reliable ECoG control of two- and three-dimensional cursor movement in less than 2 weeks and demonstrated preliminary control of a dexterous prosthetic arm [75]. This study has several characteristics worth mentioning. First, a significant portion of the ECoG grid covered the somatosensory cortex. Thus the somatosensory cortex, classically thought to be an input hub for processing sensory stimuli, was “repurposed” to act as an output hub for generating the motor control signal for BCI devices. Even though the participant has a complete spinal cord injury, he was able to reliably modulate the somatosensory cortical activity for BCI control. Second, this study was able to re-use the neural decoder across different days of BCI testing [77,78]; i.e., each testing session always started with the decoder used in the last session. This approach has several benefits: a) from a practical clinical use perspective, this greatly reduces the system setup time, and it is essentially “plug-and-go”; b) from the user training perspective, a constant decoder across training sessions can facilitate incremental learning across days by the BCI user; and c) from the BCI learning research perspective, this allows researchers to assess the retention of learned BCI control skills, which has not been characterized for BCI operation. Specifically, in the current study, the subject demonstrated comparable performance using a neural decoder learned in a previous BCI training session, and the retention of this BCI control skill spanned multiple days even with a 2-day break in between. Motivated by the short-term human study, we conducted a similar ECoG-based BCI study in a nonhuman primate [79]. The stability of the mesoscale ECoG recording made it possible for us to use a stable neural decoder without recalibration for a 4-week period, and the subject again showed the capability to retain the learned BCI control skills. Taken together, initial evidence presented here demonstrated the clinical feasibility of BCI operation based on mesoscale ECoG, as well as retention of the BCI control skill over days and weeks.

6. Advances in Engineering

6.1 Emerging Sensor Technology for Microelectrocorticography

Electrocorticography has started to gain broader acceptance in the BCI community, and as a result there continues to be a push toward smaller electrodes, particularly those in the micron range, termed microECoG [13]. These small-scale surface electrodes have seen utility in clinical studies [80] and have started to emerge in BCI applications as well [81,82], but there are a number of outstanding questions that remain regarding their long-term performance.

One of the lingering questions is how the immune reaction to these devices differs from traditional penetrating electrodes [83,84]. To begin to address this question, we began to investigate the reaction of the meningeal tissues to the continuing presence of the device. Since these reactions are primarily at the surface of the brain, we employed window imaging techniques that allow us to look longitudinally at the reaction over time [85]. We recently showed that by simply adding fenestrations to the electrode insulating layer, tissue can be elicited to grow through the device substrate [85]. We further developed “mesh electrodes” that have dielectric insulation only around individual traces, which results in a minimal electrode substrate footprint. Our initial results suggest that decreasing the areal density of

material that is implanted in the brain decreases the meningeal response to the presence of the device. We also started to integrate microfluidic channels into our microECoG devices. One of the first applications of this approach is to use microfluidic delivery of cooled fluid to modulate the temperature of the cortical surface. Taking advantage of laminar flow properties of microfluidic channels, we can selectively cool portions of the cortex in a temporally dynamic fashion. The microfluidic channels are also optically clear, which allows for simultaneous imaging, fluid delivery, and electrophysiological recording.

In the push to integrate imaging and optical stimulation, we developed mouse-scaled devices on a transparent polymer, parylene C. By implanting these arrays under a cranial window in optogenetic mice, it is possible to photostimulate the cortex next to the microECoG array. This approach has enabled us to test spatial, temporal, and spectral aspects of cortical activation and microECoG localization. Optogenetics provides a cell type-specific method to learn more about the generation of the microECoG signal, and it provides a method to test new electrode arrays. Since optogenetic stimulation creates highly repeatable, spatially and temporally defined neural signals, this platform could be used to accurately compare different microECoG designs. Optogenetics and microECoG have potential applications in the study of a number of neurological diseases (such as epilepsy) and as a bidirectional brain-computer interface.

7. Perspectives on ECoG Research and Applications/Conclusion

Electrocorticography is the technique of interrogating the brain using electrodes that are placed subdurally or epidurally. ECoG has been used for decades for select clinical purposes—most commonly to identify functional and epileptic brain areas in people with epilepsy—and occasionally for research. The important role of ECoG for basic research and its potential to create a new range of clinical applications have long been greatly underappreciated. Research over the past several years, including the work summarized in this article, has been changing this situation. While ECoG is currently, and will remain for the foreseeable future, used less prevalently than other types of imaging, its unique qualities have become widely recognized by scientists engaged in basic and translational research. Basic research suggests that ECoG can elucidate brain function in ways that cannot be readily achieved using other imaging modalities, and translational research is producing exciting new ECoG-based applications that are already becoming available in the clinic. With expected further improvements in signal acquisition and analysis, ECoG is likely to expand its utility as an important technique for characterizing normal and abnormal brain function.

Acknowledgments

This research was partially supported by the NIH [R01-NS065186 (K.J.M.) and R01-EB000856 (G.S.)] and the U.S. Army Research Office [W911NF-08-1-0216 (G.S.), W911NF-12-1-0158 (G.S.), and W911NF-12-1-0109 (G.S.)]. The authors acknowledge the invaluable assistance of Marcia Sanders in organizing and editing the text into a manageable corpus.

References

1. Miller KJ, Hermes D, Honey CJ, et al. Human motor cortical activity is selectively phase-entrained on underlying rhythms. *PLoS Comput Biol*. 2012; 8:e1002655. [PubMed: 22969416]
2. Miller KJ, Shenoy P, den Nijs M, Sorensen LB, Rao RN, Ojemann JG. Beyond the gamma band: the role of high-frequency features in movement classification. *IEEE Trans Biomed Eng*. 2008; 55:1634–7. [PubMed: 18440909]
3. Miller KJ, Leuthardt EC, Schalk G, et al. Spectral changes in cortical surface potentials during motor movement. *J Neurosci*. 2007; 27:2424–32. [PubMed: 17329441]

4. Miller KJ, Sorensen LB, Ojemann JG, den Nijs M. Power-law scaling in the brain surface electric potential. *PLoS Comput Biol.* 2009; 5:e1000609. [PubMed: 20019800]
5. Hermes D, Miller KJ, Vansteensel M, et al. Cortical theta wanes for language. *Neuroimage.* in press.
6. Kellis S, Miller K, Thomson K, Brown R, House P, Greger B. Decoding spoken words using local field potentials recorded from the cortical surface. *J Neural Eng.* 2010; 7:056007. [PubMed: 20811093]
7. Xiao R, Liao K, Ding L. Discriminating multiple motor imageries of human hands using EEG. *Conf Proc IEEE Eng Med Biol Soc.* 2012; 2012:1773–6. [PubMed: 23366254]
8. Onton J, Makeig S. High-frequency broadband modulations of electroencephalographic spectra. *Front Hum Neurosci.* 2009; 3:61. [PubMed: 20076775]
9. Miller KJ, Zanos S, Fetz EE, den Nijs M, Ojemann JG. Decoupling the cortical power spectrum reveals real-time representation of individual finger movements in humans. *J Neurosci.* 2009; 29:3132–7. [PubMed: 19279250]
10. Crone NE, Miglioretti DL, Gordon B, Lesser RP. Functional mapping of human sensorimotor cortex with electrocorticographic spectral analysis. II. Event-related synchronization in the gamma band. *Brain.* 1998; 121:2301–15. [PubMed: 9874481]
11. Leuthardt EC, Schalk G, Wolpaw JR, Ojemann JG, Moran DW. A brain-computer interface using electrocorticographic signals in humans. *J Neural Eng.* 2004; 1:63–71. [PubMed: 15876624]
12. Schalk G. Brain-computer symbiosis. *J Neural Eng.* 2008; 5:1–15. [PubMed: 18310806]
13. Thongpang S, Richner TJ, Brodnick SK, et al. A micro-electrocorticography platform and deployment strategies for chronic BCI applications. *Clin EEG Neurosci.* 2011; 42:259–65. [PubMed: 22208124]
14. Viventi J, Kim DH, Vigeland L, et al. Flexible, foldable, actively multiplexed, high-density electrode array for mapping brain activity in vivo. *Nat Neurosci.* 2011; 14:1599–605. [PubMed: 22081157]
15. Lemm S, Blankertz B, Dickhaus T, Mueller K- R. Introduction to machine learning for brain imaging. *Neuroimage.* 2011; 56:387–99. [PubMed: 21172442]
16. Parra LC, Spence CD, Gerson AD, Sajda P. Recipes for the linear analysis of EEG. *Neuroimage.* 2005; 28:326–41. [PubMed: 16084117]
17. Wolpaw, JR.; Wolpaw, EW. *Brain-computer interfaces.* Oxford University Press; New York: 2012. p. 123-46.
18. McFarland DJ, Wolpaw JR. Sensorimotor rhythm-based brain-computer interface (BCI): model order selection for autoregressive spectral analysis. *J Neural Eng.* 2008; 5:155–62. [PubMed: 18430974]
19. Asano E, Juhász C, Shah A, Sood S, Chugani HT. Role of subdural electrocorticography in prediction of long-term seizure outcome in epilepsy surgery. *Brain.* 2009; 132:1038–47. [PubMed: 19286694]
20. Palmmini A, Gambardella A, Andermann F, et al. Intrinsic epileptogenicity of human dysplastic cortex as suggested by corticography and surgical results. *Ann Neurol.* 1995; 37:476–87. [PubMed: 7717684]
21. Wong CH, Birkett J, Byth K, et al. Risk factors for complications during intracranial electrode recording in presurgical evaluation of drug resistant partial epilepsy. *Acta Neurochir (Wien).* 2009; 151:37–50. [PubMed: 19129963]
22. Brunner P, Ritaccio AL, Lynch TM, et al. A practical procedure for real-time functional mapping of eloquent cortex using electrocorticographic signals in humans. *Epilepsy Behav.* 2009; 15:278–86. [PubMed: 19366638]
23. Spencer SS. Neural networks in human epilepsy: evidence of and implications for treatment. *Epilepsia.* 2002; 43:219–27. [PubMed: 11906505]
24. Jacobs J, Zijlmans M, Zelman R, et al. High-frequency electroencephalographic oscillations correlate with outcome of epilepsy surgery. *Ann Neurol.* 2010; 67:209–20. [PubMed: 20225281]
25. Wu JY, Sankar R, Lerner JT, Matsumoto JH, Vinters HV, Mathern GW. Removing interictal fast ripples on electrocorticography linked with seizure freedom in children. *Neurology.* 2010; 75:1686–94. [PubMed: 20926787]

26. Wang S, Wang IZ, Bulacio JC, et al. Ripple classification helps to localize the seizure-onset zone in neocortical epilepsy. *Epilepsia*. 2013; 54:370–6. [PubMed: 23106394]
27. van't Klooster MA, Zijlmans M, Leijten FS, Ferrier CH, van Putten MJ, Huiskamp GJ. Time-frequency analysis of single pulse electrical stimulation to assist delineation of epileptogenic cortex. *Brain*. 2011; 134:2855–66. [PubMed: 21900209]
28. McIntyre CC, Savasta M, Kerkerian-Le Goff L, Vitek JL. Uncovering the mechanism(s) of action of deep brain stimulation: activation, inhibition, or both. *Clin Neurophysiol*. 2004; 115:1239–48. [PubMed: 15134690]
29. Tehovnik EJ, Tolias AS, Sultan F, Slocum WM, Logothetis NK. Direct and indirect activation of cortical neurons by electrical microstimulation. *J Neurophysiol*. 2006; 96:512–21. [PubMed: 16835359]
30. Rattay F. The basic mechanism for the electrical stimulation of the nervous system. *Neuroscience*. 1999; 89:335–46. [PubMed: 10077317]
31. Gradinaru V, Mogri M, Thompson KR, Henderson JM, Deisseroth K. Optical deconstruction of parkinsonian neural circuitry. *Science*. 2009; 324:354–9. [PubMed: 19299587]
32. Logothetis NK, Augath M, Murayama Y, et al. The effects of electrical microstimulation on cortical signal propagation. *Nat Neurosci*. 2010; 13:1283–91. [PubMed: 20818384]
33. Tolias AS, Sultan F, Augath M, et al. Mapping cortical activity elicited with electrical microstimulation using fMRI in the macaque. *Neuron*. 2005; 48:901–11. [PubMed: 16364895]
34. Borchers S, Himmelbach M, Logothetis N, Karnath HO. Direct electrical stimulation of human cortex--the gold standard for mapping brain functions? *Nat Rev Neurosci*. 2012; 13:63–70. [PubMed: 22127300]
35. Selimbeyoglu A, Parvizi J. Electrical stimulation of the human brain: perceptual and behavioral phenomena reported in the old and new literature. *Front Hum Neurosci*. 2010; 4:46. [PubMed: 20577584]
36. Parvizi J, Jacques C, Foster BL, et al. Electrical stimulation of human fusiform face-selective regions distorts face perception. *J Neurosci*. 2012; 32:14915–20. [PubMed: 23100414]
37. Bejjani BP, Damier P, Arnulf I, et al. Transient acute depression induced by high-frequency deep-brain stimulation. *N Engl J Med*. 1999; 340:1476–80. [PubMed: 10320386]
38. Parvizi J. Corticocentric myopia: old bias in new cognitive sciences. *Trends Cogn Sci*. 2009; 13:354–9. [PubMed: 19595625]
39. Penfield, W.; Jasper, H. *Epilepsy and the Functional Anatomy of the Human Brain*. Little, Brown; Boston, MA: 1954.
40. Worrell G, Parish L, Cranstoun SD, Jonas R, Baltuch G, Litt B. High-frequency oscillations and seizure generation in neocortical epilepsy. *Brain*. 2004; 127:1496–506. [PubMed: 15155522]
41. Morrell MJ. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology*. 2011; 77:1295–304. [PubMed: 21917777]
42. Fisher R, Salanova V, Witt T, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia*. 2010; 51:899–908. [PubMed: 20331461]
43. Bower MR, Stead M, Meyer FB, Marsh WR, Worrell G. Spatiotemporal neuronal correlates of seizure generation in focal epilepsy. *Epilepsia*. 2012; 53:807–16. [PubMed: 22352423]
44. Truccolo W, Donoghue JA, Hochberg LR, Eskandar EN, Madsen JR, Anderson WS, et al. Single-neuron dynamics in human focal epilepsy. *Nat Neurosci*. 2011; 14:635–41. [PubMed: 21441925]
45. Cook MJ, O'Brien TJ, Berkovic SF, Murphy M, Morokoff A, Fabinyi G, et al. Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study. *Lancet Neurol*. 2013; 12:563–71. [PubMed: 23642342]
46. Davis KA, Sturges BK, Vite CH, Ruedebusch V, Worrell G, Gardner AB, et al. A novel implanted device to wirelessly record and analyze continuous intracranial canine EEG. *Epilepsy Res*. 2011; 96:116–22. [PubMed: 21676591]
47. Ritaccio A, Boatman-Reich D, Brunner P, et al. Proceedings of the second international workshop on advances in electrocorticography. *Epilepsy Behav*. 2011; 22:641–50. [PubMed: 22036287]
48. Crone NE, Korzeniewska A, Franaszczuk PJ. Cortical gamma responses: searching high and low. *Int J Psychophysiol*. 2011; 79:9–15. [PubMed: 21081143]

49. Schalk G, Brunner P, Gerhardt LA, Bischof H, Wolpaw JR. Brain-computer interfaces (BCIs): detection instead of classification. *J Neurosci Methods*. 2008; 167:51–62. [PubMed: 17920134]
50. Schalk G, Leuthardt EC, Ojemann JG, Gerhardt LA, Wolpaw JR. Real-time detection of event-related brain activity. *Neuroimage*. 2008; 43:245–9. [PubMed: 18718544]
51. Schalk G, McFarland DJ, Hinterberger T, Birbaumer N, Wolpaw JR. BCI2000: a general-purpose brain-computer interface (BCI) system. *IEEE Trans Biomed Eng*. 2004; 51:1034–43. [PubMed: 15188875]
52. Roland J, Brunner P, Johnston J, Schalk G, Leuthardt EC. Passive real-time identification of speech and motor cortex during an awake craniotomy. *Epilepsy Behav*. 2010; 18:123–8. [PubMed: 20478745]
53. Crone NE, Sinai A, Korzeniewska A. High-frequency gamma oscillations and human brain mapping with electrocorticography. *Prog Brain Res*. 2006; 159:275–95. [PubMed: 17071238]
54. Lachaux JP, Rudrauf D, Kahane P. Intracranial EEG and human brain mapping. *J Physiol Paris*. 2003; 97:613–28. [PubMed: 15242670]
55. Conner CR, Ellmore TM, DiSano MA, et al. Anatomic and electro-physiologic connectivity of the language system: a combined DTI-CCEP study. *Comput Biol Med*. 2011; 41:1100–9. [PubMed: 21851933]
56. Lachaux JP, Chavez M, Lutz A. A simple measure of correlation across time, frequency and space between continuous brain signals. *J Neurosci Methods*. 2003; 123:175–88. [PubMed: 12606066]
57. Alivisatos AP, Andrews AM, Boyden ES, et al. Nanotools for neuroscience and brain activity mapping. *ACS Nano*. 2013; 7:1850–66. [PubMed: 23514423]
58. Pieters TA, Conner CR, Tandon N. Recursive grid partitioning on a cortical surface model: an optimized technique for the localization of implanted subdural electrodes. *J Neurosurg*. 2013; 118:1086–97. [PubMed: 23495883]
59. Logothetis NK, Wandell BA. Interpreting the BOLD signal. *Annu Rev Physiol*. 2004; 66:735–69. [PubMed: 14977420]
60. Conner CR, Ellmore TM, Pieters TA, DiSano MA, Tandon N. Variability of the relationship between electrophysiology and BOLD-fMRI across cortical regions in humans. *J Neurosci*. 2011; 31:12855–65. [PubMed: 21900564]
61. Ojemann GA, Ojemann J, Ramsey NF. Relation between functional magnetic resonance imaging (fMRI) and single neuron, local field potential (LFP) and electrocorticography (ECoG) activity in human cortex. *Front Hum Neurosci*. 2013; 7:34. [PubMed: 23431088]
62. Tertel K, Tandon N, Ellmore TM. Probing brain connectivity by combined analysis of diffusion MRI tractography and electrocorticography. *Comput Biol Med*. 2011; 41:1092–9. [PubMed: 21129738]
63. Buxton RB, Uluda K, Dubowitz DJ, Liu TT. Modeling the hemodynamic response to brain activation. *Neuroimage*. 2004; 23(Suppl 1):S220–33. [PubMed: 15501093]
64. Ramsey NF, Hoogduin H, Jansma JM. Functional MRI experiments: acquisition, analysis and interpretation of data. *Eur Neuropsychopharmacol*. 2002; 12:517–26. [PubMed: 12468015]
65. Turner R. How much cortex can a vein drain? Downstream dilution of activation-related cerebral blood oxygenation changes. *Neuroimage*. 2002; 16:1062–7. [PubMed: 12202093]
66. Siero JC, Ramsey NF, Hoogduin H, Klomp DW, Luijten PR, Petridou N. BOLD specificity and dynamics evaluated in humans at 7 T: comparing gradient-echo and spin echo hemodynamic responses. *PLoS One*. 2013; 8:e54560. [PubMed: 23336008]
67. Lachaux JP, Fonlupt P, Kahane P, et al. Relationship between task-related gamma oscillations and BOLD signal: new insights from combined fMRI and intracranial EEG. *Hum Brain Mapp*. 2007; 28:1368–75. [PubMed: 17274021]
68. Hermes D, Miller KJ, Vansteensel MJ, Aarnoutse EJ, Leijten FS, Ramsey NF. Neurophysiologic correlates of fMRI in human motor cortex. *Hum Brain Mapp*. 2012; 33:1689–99. [PubMed: 21692146]
69. Hermes D, Siero JC, Aarnoutse EJ, Leijten FS, Petridou N, Ramsey NF. Dissociation between neuronal activity in sensorimotor cortex and hand movement revealed as a function of movement rate. *J Neurosci*. 2012; 32:9736–44. [PubMed: 22787059]

70. Siero JC, Hermes D, Hoogduin H, Luijten PR, Petridou N, Ramsey NF. BOLD consistently matches electrophysiology in human sensorimotor cortex at increasing movement rates: a combined 7T fMRI and ECoG study on neurovascular coupling. *J Cereb Blood Flow Metab.* in press.
71. Petridou N, Italiaander M, van de Bank BL, Siero JC, Luijten PR, Klomp DW. Pushing the limits of high-resolution functional MRI using a simple high-density multi-element coil design. *NMR Biomed.* 2013; 26:65–73. [PubMed: 22674638]
72. Schalk G, Miller KJ, Anderson NR, et al. Two-dimensional movement control using electrocorticographic signals in humans. *J Neural Eng.* 2008; 5:75–84. [PubMed: 18310813]
73. Rouse AG, Stanslaski SR, Cong P, et al. A chronic generalized bi-directional brain-machine interface. *J Neural Eng.* 2011; 8:036018. [PubMed: 21543839]
74. Rouse AG, Williams JJ, Wheeler JJ, Moran DW. Cortical adaptation to a chronic micro-electrocorticographic brain computer interface. *J Neurosci.* 2013; 33:1326–30. [PubMed: 23345208]
75. Wang W, Collinger JL, Degenhart AD, et al. An electrocorticographic brain interface in an individual with tetraplegia. *PLoS One.* 2013; 8:e55344. [PubMed: 23405137]
76. Miller KJ, Schalk G, Fetz EE, den Nijs M, Ojemann JG, Rao RP. Cortical activity during motor execution, motor imagery, and imagery-based online feedback. *Proc Natl Acad Sci USA.* 2010; 107:4430–5. [PubMed: 20160084]
77. Ganguly K, Carmena JM. Emergence of a stable cortical map for neuroprosthetic control. *PLoS Biol.* 2009; 7:e1000153. [PubMed: 19621062]
78. Blakely T, Miller KJ, Zanos SP, Rao RP, Ojemann JG. Robust, long-term control of an electrocorticographic brain-computer interface with fixed parameters. *Neurosurg Focus.* 2009; 27:E13. [PubMed: 19569888]
79. Ashmore, RC.; Endler, BM.; Smalianchuk, I., et al. IEEE EMBC. San Diego, CA: 2012. Stable online control of an electrocorticographic brain-computer interface using a static decoder..
80. Stead M, Bower M, Brinkmann BH, et al. Microseizures and the spatiotemporal scales of human partial epilepsy. *Brain.* 2010; 133:2789–97. [PubMed: 20685804]
81. Leuthardt E, Freudenberg Z, Bundy D, Roland J. Microscale recording from human motor cortex: implications for minimally invasive electrocorticographic brain-computer interfaces. *Neurosurg Focus.* 2009; 27:E10. [PubMed: 19569885]
82. Rouse AG, Moran DW. Neural adaptation of epidural electrocorticographic (eecog) signals during closed-loop brain computer interface (BCI) tasks. *Conf Proc IEEE Eng Med Biol Soc.* 2009; 2009:5514–7. [PubMed: 19964124]
83. Sillay KA, Rutecki P, Cicora K, et al. Long-term measurement of impedance in a large series of chronically implanted depth and cortical strip electrodes during responsive neurostimulation in humans. *Brain Stimul.* in press.
84. Williams JC, Hippensteel JA, Dilgen J, Shain W, Kipke DR. Complex impedance spectroscopy for monitoring tissue responses to inserted neural implants. *J Neural Eng.* 2007; 4:410–23. [PubMed: 18057508]
85. Schendel AA, Thongpang S, Brodnick SK, et al. A cranial window imaging method for monitoring vascular growth around chronically implanted micro-ECoG devices. *J Neuroscience Methods.* 2013; 218:121–30.

Highlights

- Basic research suggests that ECoG can elucidate brain function in ways that cannot be readily achieved using other imaging modalities.
- Translational research is producing ECoG-based applications that are beginning to be available in the clinic.
- There is great potential for continuing improvements in signal acquisition, signal analysis, and interpretation of ECoG signals.
- ECoG is increasingly recognized for its important value for characterizing normal and abnormal brain function.

Figure 1.

Spectral decomposition in electrocorticography. (A) The distribution of broadband ECoG activity during thumb movement compared with rest in a single subject (color indicates r^2 values, maximum 0.76 at circled site). Adapted from Miller et al. [1]. (B) PSD from circle site in (A), log scale on y-axis. Green band: 8–32 Hz; orange band: 76–100 Hz (60-Hz line noise and harmonics excluded); gray denotes movements of the 2nd–5th digits. (C) Two-dimensional feature space for HFB-LFB log power. Insets on each axis denote mean of power (error bar ± 3 SEM) during thumb (red) and finger (gray) movement, as well as rest (x-axis, error bar in middle). Brown axes represent principal axes after singular value decomposition, with PSC projection weights, sorted by movement/rest shown at insets on axes. (D) Projection vector weights from first 3 PSCs for decomposition using log power at each Hz. Insets show projection weights for PSC 1 (pink) and 2 (orange). See Miller et al. [9] for full description. (E&F) Reconstructed PSDs using subsets of the PSCs.

Figure 2.

Left panel illustrates the concept and workflow of real-time functional brain mapping. BCI2000 software applies the SIGFRIED method to detect task-related changes and maps results in real time onto the subject-specific anatomic model (E). Right panel presents exemplary results from one subject. See text for detailed explanation.

Figure 3.

A conjunction analysis and representation of group verb and noun naming versus scrambled results (n = 19) thresholded at a corrected $p < 0.05$ and visualized to identify regions active during either one or both tasks.

Figure 4.
Postoperative X-ray image showing the high-density mesoscale ECoG electrode grid implanted in an individual with tetraplegia.

Table 1

Established and novel ECoG applications

<i>Clinical</i>
Ictal/interictal recording
Pathologic oscillation recording
Seizure detection/prediction
Seizure termination (electrical, thermal)
Seizure stimulation
Electrical stimulation functional mapping (ESM)
Passive real-time functional mapping
<i>Research</i>
Cognitive and systems neuroscience (sensorimotor, language, auditory, attention, visual)
Multimodal relationships (e.g., with fMRI, ESM)
Neuroprosthetics/brain-computer interface
Communication functions (language prediction and synthetic production)