Proceedings of the Eighth International Workshop on Advances in Electrocorticography

Anthony L. Ritaccio [a,*], Justin Williams [b], Tim Denison [c], Brett L. Foster [d], Philip A. Starr [e], Aysegul Gunduz [f], Maeike Zijlmans [g,h], Gerwin Schalk [a,i]

[a] Albany Medical College, Albany, NY, USA
[b] University of Wisconsin-Madison, Madison, WI, USA
[c] Medtronic Neuromodulation, Minneapolis, MN, USA
[d] Stanford University, Mountain View, CA, USA
[e] University of California, San Francisco, CA, USA
[f] University of Florida, Gainesville, FL, USA
[g] University Medical Center Utrecht, Utrecht, The Netherlands
[h] Stichting Epilepsie Instellingen Nederland, Heemstede, The Netherlands
[i] Wadsworth Center, New York State Department of Health, Albany, NY, USA

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ABSTRACT

Excerpted proceedings of the Eighth International Workshop on Advances in Electrocorticography (ECoG), which convened October 15–16, 2015 in Chicago, IL, are presented. The workshop series has become the foremost gathering to present current basic and clinical research in subdural brain signal recording and analysis.

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1. Introduction

A. Ritaccio

The Eighth International Workshop on Advances in Electrocorticography (ECoG) took place on October 15–16, 2015, in Chicago, IL. The workshop series, now in its seventh year, has had the annual opportunity to present its proceedings to the readership of *Epilepsy & Behavior* since its inception. As found by a recent Scopus search, nearly one-third of ECoG-related research publications in peer-reviewed journals over the past decade have been authored by past and present faculty of this meeting. The Eighth International Workshop contained 16 authoritative research presentations and reviews over a compact 2-day gathering. Advances in engineering and in the use of ECoG for the detection of disease states represented the most novel content, and we have decided to excerpt these in this summary document.

* Corresponding author at: Department of Neurology, Albany Medical College, Albany, NY, USA.
E-mail address: RitaccA@mail.amc.edu (A.L. Ritaccio).

2. Engineering

2.1. Advanced materials for thin-film microECoG devices

Justin Williams

There has been a push over the last decade in the development of microECoG devices that are based on thin-film microfabrication processes. This has resulted in a number of studies that utilize various flexible polymers as the insulating substrate for microfabricated devices to record high-resolution activity from the surface of the brain [1]. Although much work has been put into making insulating substrates more flexible, little attention has been given to the electrode elements because of the intrinsic flexibility of most metallic conductors and their extremely thin cross-section due to metallic deposition techniques.

With the advent of new genetic engineering approaches, there also has been increased interest in devices that are compatible with optical imaging and stimulation techniques. It is now commonplace to use transgenic animal models that express genetically encoded proteins that allow for optical activation or optical imaging of neurons in the

living brain [2]. As a result, numerous studies have been developed to integrate neural recording devices with optical delivery methods. These approaches all suffer from utilizing traditional insulators and conductors that are either optically opaque or made of semiconductors that produce optical artifacts. More recently, investigators have started to explore methods to incorporate optically clear conductors in an attempt to produce devices that do not interfere with optical imaging and modulation.

One of the recent approaches has been to incorporate single crystal graphene sheets as the conducting elements of implantable microECoG electrodes [3]. Graphene is not only optically transparent but also highly conductive as well as extremely flexible. It also has a uniform transparency across a wide range of the optical spectrum, making it applicable to a variety of imaging and optical stimulation techniques, from optogenetic modulation of channel rhodopsin with blue light to multi-photon imaging with infrared light [2]. Graphene is part of a class of newly developed materials classified as "2D" materials, which take on exceptional new properties as one of their dimensions approaches atomic levels [3]. These types of materials have recently been explored in other neural engineering applications for interfacing with single neurons in culture, because they can be formed into self-rolling tubes that mimic the size and the mechanical and electrical properties of the natural myelin sheath that normally insulates axons [4]. These examples foreshadow the potential for utilizing other 2D materials in future neural interface applications.

3. Basic science

3.1. The application of "brain–machine-interfacing" to neuromodulation: enabling an evolutionary and translational prosthetics roadmap?

Tim Denison

Modulating neural activity through stimulation is an effective treatment not only for epilepsy but also for several other neurological diseases such as Parkinson's disease and essential tremor. Opportunities for improving modulation of neural activity include reducing the burden of optimizing stimulation parameters, objectively measuring efficacy over time, and continuously adjusting therapy to optimize patient outcomes [5]. Achieving these goals is challenging given several practical issues, including the paucity of human data related to disease states, poorly validated patient state estimators, and evolving nonlinear mappings between estimated patient state and optimal stimulation parameters.

The application of brain–machine-interface (BMI) technology to existing stimulator architectures could help address these issues and potentially enable smarter future "prosthesis" systems for neural circuits impacted by disease. Referencing Fig. 1, we developed an investigational, implantable, bidirectional neural interface system based on commercially released device architectures [5]. The research system provides stimulation therapy while simultaneously recording and classifying physiological signals from neural circuits [6]. The modularity of the system provides investigational access to both cortical and subcortical circuits simultaneously, which can facilitate the dynamic characterization of brain networks, their relationship to disease, and how stimulation impacts these dynamics. To aid in the integration of the physiology and hardware, the architecture connects the implanted sensing and stimulation pathways with externalized algorithms, which are performed in a local computer and linked via telemetry [7]. The use of a distributed architecture allows for interactive prototyping of both classification algorithms for diagnostics and dynamic actuation controllers for exploring closed-loop operation. As the understanding of the neural system matures, the implant can be wirelessly upgraded for completely embedded operation, self-contained in the implant [8].

The bidirectional BMI research system is currently deployed with investigator-sponsored clinical studies worldwide. Two examples of research using the tool were discussed at this workshop (vide infra): Dr. Philip Starr discussed exploring movement disorder circuits with an emphasis on Parkinson's disease, and Dr. Aysegul Gunduz discussed exploring networks associated with Tourette disease. In each case, physiological markers correlated with clinical state are informing classification algorithms and dynamic actuation controllers. In general, the process involves two stages: first, characterizing the network transfer function and training the classifier by sensing the physiological response to stimulation or pharmaceuticals, and then second, applying these functions as the basis for a dynamic closed-loop algorithm [8].

From a practical point of view, and as demonstrated by the investigational work described at the workshop, neuromodulation therapies offer a unique and practical opportunity for *translating* ECoG BMI technologies into a clinical research setting [9]. Several neurological disease treatments apply invasive device stimulation therapies, and the addition of sensing and algorithm technology is an obvious *evolutionary* expansion of capabilities if the benefits of the capability clearly offset any incremental risks or costs. While initial investigational applications are focused on epilepsy and movement disorders, the technology is potentially transferable to a broader base of disorders, including stroke and rehabilitation.
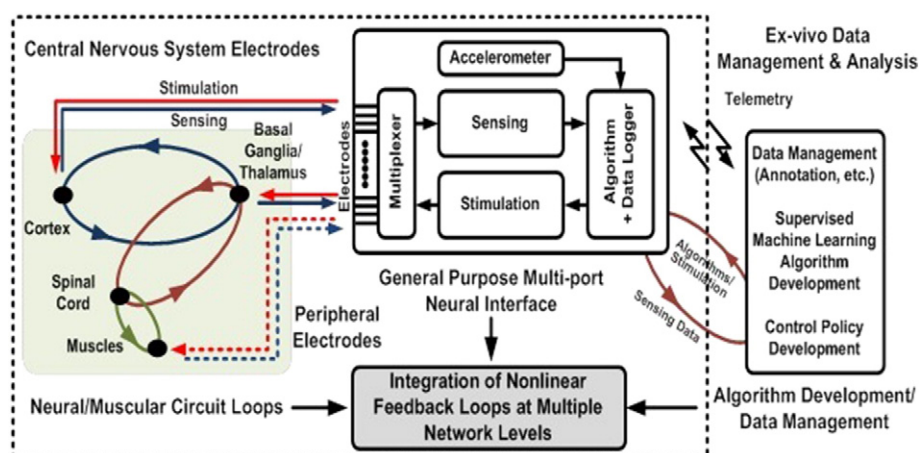

Fig. 1. Block diagram of the investigational research system being used to characterize cortical and subcortical neural networks in human disease. See work by Starr (Section 4.1) and Gunduz (Section 4.2) for representative examples of its use.

3.2. Electrocorticography of human parietal cortex during episodic memory retrieval

Brett L. Foster

A large body of evidence from neuroimaging suggests that subregions of the human parietal lobe contribute to episodic memory retrieval. During successful retrieval, posterior cingulate (PCC) and retrosplenial cortices (RSC) on the medial surface and the angular gyrus (AG) on the lateral surface display robust coactivation. Furthermore, these parietal subregions are part of a large-scale network, the default network, which includes core mnemonic regions such as the hippocampus and parahippocampal cortex.

Our group has utilized unique opportunities provided by ECoG to study the cognitive electrophysiology of the human medial parietal cortex (MPC). The invasive nature of ECoG recordings is particularly salient for this research program, as the ability to obtain reliable spatio-temporal signals from medial cortices hidden within the interhemi-spheric fissure is exceptionally difficult through noninvasive measures (e.g., electroencephalography, EEG). By using multisite ECoG recordings, we studied how the MPC, as a core node of the default network, is engaged during episodic memory retrieval and how this region interacts with other network nodes.

Initial human ECoG investigations suggested that ventral regions of the MPC, such as the RSC and much of the PCC, display selective electrocortical activation (increased high-frequency broadband power, HFB: 70–180 Hz) during episodic (autobiographical) retrieval [10]. These initial observations were replicated and extended to show activation of RSC/PCC in both the left and right MPC during autobiographical retrieval [11]. Analysis of HFB response timing during retrieval showed MPC regions to have a late onset (~630 ms), suggesting a dependency on computations in other regions [11].

To explore network interactions, we first focused on dynamic synchrony between MPC and the medial temporal lobe (MTL) during retrieval. Based on previous observations of prominent theta oscillations in the MPC [12], akin to those observed in the MTL, we studied theta phase synchrony between MPC and MTL. Consistent with previous work, we found that selective theta phase synchrony in the range of 3–5 Hz occurred between MPC and MTL subregions only during autobiographical retrieval [13]. This transient synchrony always preceded the maximal engagement of MPC HFB activity, consistent with our previous observations of late response onset in MPC.

Most recently, we have focused on studying interactions within the parietal lobe, between medial and lateral subregions. Consistent with a wide body of work from human neuroimaging, we observed selective correlation of single-trial HFB responses between RSC/PCC and AG during retrieval. Strikingly, we found that these regions had near-simultaneous HFB response onset times during retrieval, suggesting a shared input to both regions, potentially from the MTL. By studying slow (<1 Hz) intrinsic fluctuations of HFB activity, we also observed similar correlation patterns between medial and lateral parietal subregions during resting and sleeping states, matching functional magnetic resonance imaging (fMRI) data from each subject (Fig. 2). These multisite recordings provide some of the first evidence for the basic electrocortical correlates of task and resting-state connectivity commonly observed with human fMRI.

4. Translational

4.1. Electrocorticography during surgery for movement disorders: insights into circuit mechanisms

Philip A. Starr

There is great interest in the theory that abnormal oscillatory activity in the basal ganglia-thalamocortical circuit is the basis for the signs and symptoms of movement disorders, especially in Parkinson's disease (PD) [14]. Until recently, however, most analyses in humans have
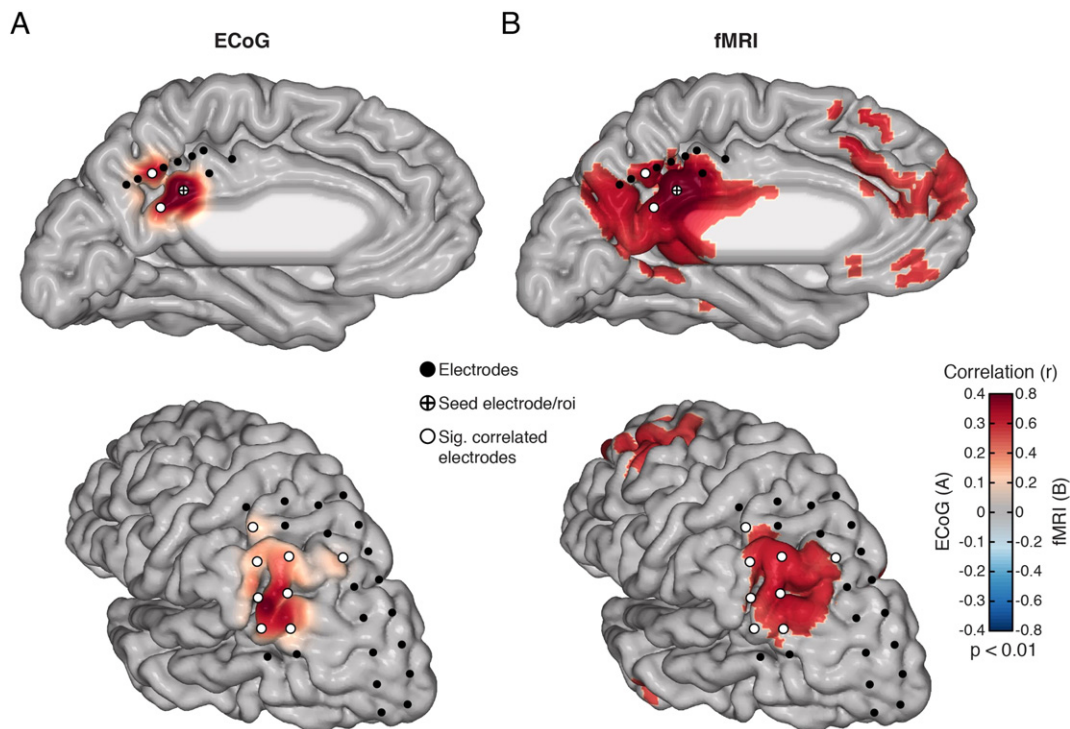

Fig. 2. Similarity of ECoG and fMRI resting-state connectivity. (A) Resting-state ECoG data are shown for an example PCC seed electrode. Based on the seed region in PCC, slow (<1 Hz) HFB amplitude is correlated significantly and selectively with AG (significant electrodes show white fill color). (B) Resting-state fMRI data are shown for the same seed location but with full brain voxel-wise correlation. Electrocorticography electrode locations are overlaid to show correspondence between modalities, whereby significantly correlated electrodes colocate with significantly correlated voxel clusters.
[Adapted from Foster et al. (2015).]

been performed using low-amplitude basal ganglia local field potentials (LFPs). Because these are recorded from intraparenchymal electrodes, for ethical reasons, the use of LFP recordings for research is restricted to clinically indicated targets, which vary between disease states. Electrocorticography presents an alternative method to access a critical structure in the basal ganglia-thalamocortical motor loop, the primary motor cortex, for analyses of oscillatory activity or local neuronal activation as assessed by task-related changes in broadband gamma activity. Electrocorticography can be readily performed intraoperatively in awake patients during deep brain stimulator implantation in PD, isolated dystonia, and essential tremor. Advantages of ECoG, compared with basal ganglia LFPs, include signal strength, measurement of population spiking via broadband gamma analysis, low stimulation artifact during deep brain stimulation (DBS), and potential to record from the same brain region across multiple disease states. Electrocorticography can be performed during DBS implantation surgery without additional surgical exposure or additional parenchymal penetration. We have safely utilized ECoG as a research tool during movement disorder surgery in over 200 cases [15].

Oscillatory synchronization of cortical population spiking can be analyzed by examining the extent to which broadband gamma activity occurs at a specific phase of low-frequency rhythms, such as the beta rhythm. This interaction, phase–amplitude coupling (PAC), has attracted great interest as a normal mechanism in human cortical function, linking long-range oscillatory synchronization with local cortical processing [16]. We have shown that, in PD, PAC in primary motor cortex is elevated compared with nonparkinsonian conditions, including humans without movement disorders undergoing motor cortex ECoG in an epilepsy monitoring unit [17]. Further, acute therapeutic DBS reversibly reduces elevated motor cortex PAC in PD, with a time course similar to that of stimulation-induced improvement in motor symptoms, without altering the amplitude of beta- or gamma-band activity [18]. We propose that excessive phase locking of motor cortical neurons in PD restricts neuronal pools in an inflexible pattern of activity, that this is the basis for akinesia in PD, and that the mechanism of therapeutic DBS is the decoupling of cortical population spiking from the motor beta rhythm.

4.2. Neural correlates of Tourette syndrome in the human thalamocortical network

Aysegul Gunduz

Tourette syndrome (TS) is a paroxysmal neuropsychiatric disorder characterized by involuntary movements and vocal outbursts known as tics. The exact causes of TS remain unknown; however, recent neuropathology studies have collectively implicated dysfunction of corticostriatal and thalamocortical circuits. These brain areas are thought to play a substantive role in the generation of abnormal motor programs, possibly because of excessive disinhibition of the thalamus [19]. Because of the lack of an ideal animal model and relatively normal neuroanatomy, the collection of neural activity from awake and behaving human subjects with TS will offer new and vital insights into the underlying neurophysiology of tic generation.

Deep brain stimulation is an emerging therapy for cases of severe and intractable Tourette syndrome. It is an invasive neuromodulatory therapy in which depth electrodes are placed within deep subcortical structures of the brain and high-frequency electrical stimulation is used to modulate pathological neural activity. The DBS surgery facilitates an opportunity to record electrophysiology from the implanted depth electrodes, as well as acute replacement of ECoG strips to study the network effects of pathology [20]. The use of ECoG strips also facilitates the study of the effects of DBS on the cortex [18]. For instance, ECoG strips over the motor cortex can elucidate how DBS mitigates motor symptoms. Moreover, next-generation DBS devices now allow chronic recording of neural activity from the target subcortical structures, as well as ECoG strips [6].

We addressed the gaps in knowledge in TS pathology by chronically recording neural activity from the centromedian–parafascicular (Cm-Pf) complex of the thalamus and the hand motor cortex bilaterally. The ECoG strips were placed using somatosensory-evoked potentials [21] and real-time functional mapping [22] during awake DBS surgery. Our long-term studies have revealed pathological low-frequency activity (nonoscillatory deflections in the raw potential) in the Cm-Pf during tics, not present during voluntary movements [23]. Moreover, PAC analysis revealed increased alpha phase–high gamma amplitude coupling over the motor cortex with therapeutic DBS, which was absent at baseline and during/after nontherapeutic DBS [23]. Overall, our studies show that ECoG as a signal modality can be very useful for understanding and treating neurological disorders beyond epilepsy.

5. Clinical

5.1. Epileptic spikes and high-frequency oscillations in the electrocorticogram

M. Zijlmans

Neurologists estimate the epileptogenic zone during presurgical long-term ECoG recording by assessing seizures and interictal epileptiform discharges or spikes during presurgical evaluation and try to separate epileptogenic tissue from functionally eloquent cortex. Epileptic high-frequency oscillations (HFOs) are potential new biomarkers that are more specific for the seizure onset zone than spikes and may be even better predictors for surgical outcome than the seizure onset zone [24]. The HFOs are divided into ripples of 80 to 250 Hz and fast ripples of 250 to 500 Hz. Fast ripples seem more specific for epileptogenic tissue than ripples [24]. High-frequency oscillations can co-occur with spikes and occur independently. Normal brain tissue put into epileptogenic circumstances does not produce fast ripples. This underlines that fast ripples are true biomarkers of epileptogenic tissue, and in my view, spikes represent the brain's network response to the diseased tissue. A proposed hypothesis on the pathophysiology of fast ripples is out-of-phase firing of groups of hypersynchronously firing excitatory principal neurons [25].

Most studies on HFOs have relied on depth EEG, but their findings were confirmed by long-term ECoG findings. One study found that fast ripples in the prerestriction *intraoperative* ECoG could predict postsurgical outcome [26]. We found that residual fast ripples, but not ripples, spikes, or ictiform spike patterns, in *postresection* intraoperative ECoG predict seizure recurrence after epilepsy surgery [27]. The preliminary comparison of prerestriction and postresection ECoG suggests that the best predictors of outcome are postresection fast ripples, given the presence of prerestriction fast ripples. For clinical purposes, recording the postresection ECoG thus seems essential to evaluate if the whole fast ripple zone is removed. We found that new spikes could appear at the resection border, which is a warning for "spike hunting", whereas this was not found for HFOs. We started a prospective randomized trial to study the use of HFOs compared with spikes during surgery. For onsite use of HFOs, it is important to stop propofol, to focus on the clinical question, and to be able to distinguish epileptic HFOs from physiological HFOs and artifacts. Signal analysis methods might aid this process.

Multiple papers report physiological HFOs or high frequency activity, especially in mesiotemporally placed electrodes, related to memory, and in the occipital lobe and the sensorimotor areas. In our experience with ECoG, we seem to record physiological HFOs, especially ripples, in functionally eloquent areas such as the visual cortex, sensorimotor cortex, and language areas. We have had few recordings of ripples in the sensorimotor area which increased after a successful resection of epileptogenic tissue, suggesting that removing the pathological area in the epileptic network yielded an increase in physiological activity elsewhere [28]. Physiological HFOs usually are of longer duration than pathological HFOs and do not co-occur with spikes. Signal analysis methods

might also aid in the differentiation of epileptic HFOs and physiological high frequency activity.

6. Perspectives/conclusion

G. Schalk

Basic and applied ECoG-related research has matured substantially over the past decade. About 10 years ago, only a select number of scientists were engaged in primary ECoG-related research. Electrocorticography-related presence at conferences was sparse and was often met with skepticism. Since then, research output has increased dramatically and has begun to occur in progressively larger areas of cognitive and systems neuroscience. In addition, ECoG has been receiving increasing attention at neuroscientific conferences, including the dedicated ECoG conference series whose lectures are the subject of the present review. As a result of these increasingly proliferate, sophisticated, and impactful research and dissemination activities, ECoG has become commonly accepted as an important electrophysiological imaging technique and is now widely recognized and valued for its unique properties.

This recognition of the ECoG platform is appropriate and encouraging. At the same time, it is becoming increasingly clear that the existing conceptual and technical frameworks that guide and implement ECoG-based research protocols are painfully inadequate. This is the case in basic research, in which investigators are only barely beginning to take full advantage of ECoG's unique abilities, as well as in translational research, in which interrogation of the brain that seeks to diagnose or treat nervous system disorders is following mostly static and relatively arbitrary protocols. With the further necessary and expected improvements in these areas, the value of ECoG for basic and translational neuroscience is likely going to continue to increase substantially. The present review summarizes some of the best current examples of important work in this area.

Acknowledgments

Conflict of interest

T. Denison is an employee and shareholder of Medtronic PLC, which developed the investigational systems discussed. There are no known conflicts of interest associated with this publication, and there has been no significant financial support for this work that could have influenced its outcome.

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