ECoG-Based BCIs

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Abstract

This chapter reviews the state of the art of brain–computer interfaces (BCIs) that use electrocorticography (ECoG) signals as an input. We first present the clinical settings and signal acquisition systems, including subdural grid electrodes, that lend themselves to ECoG data collection. Second, we discuss the current understanding of ECoG signal physiology and ECoG features that cannot be captured by noninvasive electrophysiology or imaging, and how this knowledge can be translated to signal features that can control BCIs. Next, we review ECoG-based BCIs in the literature that enable control, communication, and therapeutic neuromodulation. This is followed by a review of current implantable ECoG device technologies approved or available for investigational use in humans. Finally, we present and discuss various open questions in the field of ECoG BCIs and future research directions that may lead to the translation of these technologies into clinical practice.

16.1 INTRODUCTION

Electrocorticography (ECoG) is an electrophysiological technique that utilizes electrodes placed intracranially on the surface of the brain. ECoG has been employed in humans clinically for over six decades for the localization of epileptic zones and for functional brain mapping. However, its value for basic human neuroscientific research and its potential to enable new translational applications had not been widely recognized until recently. ECoG signals are captured either above (epidural) or below (subdural) the dura mater, but not within the brain tissue itself (see Figure 16.1). Many studies over the last decade have demonstrated the functional specificity, signal fidelity, and long-term stability of ECoG activity in behavioral and cognitive tasks (Schalk 2010). Together with its spatial and temporal resolution and coverage of distant areas of the brain, these unique qualities suggest that ECoG elucidates brain function in ways that cannot be achieved by other electrophysiological or neuroimaging techniques. For instance, intracortical electrode recordings usually have issues with long-term stability; scalp-recorded EEG lacks functional specificity and is very prone to artifacts; and metabolic responses captured via neuroimaging may be too slow for practical applications.
This chapter focuses on ECoG-based brain–computer interface (BCI) development as an exciting and important area in clinical translation in humans. It has four major sections. The first section addresses signal acquisition methods to capture ECoG signals. The second section examines the emerging understanding of ECoG physiology and the ECoG signal features that form the basis for BCI applications. The third section examines current BCI applications that utilize ECoG signals for computer/machine control, for communication, and for neuromodulation in neurological disorders. The fourth and final section discusses the limitations of and open questions in ECoG-based BCI development and suggests how ongoing ECoG studies, such as investigations of optimal electrode configurations (size and spacing) and investigations of signal quality of epidurally recorded ECoG, are likely to facilitate the feasibility of ECoG-based BCIs outside the clinic.

16.2 ECoG SIGNAL ACQUISITION

Penfield’s pioneering work in the 1950s with epilepsy patients represented the first comprehensive ECoG-based effort to study the neural basis of human behavior (Penfield and Rasmussen 1950). To this date, the large majority of human ECoG studies have been restricted to neurosurgical patients since the collection of ECoG signals requires surgery that consists of a craniotomy, followed by an incision to the protective dura matter for the placement of electrode arrays on the cortical surface. ECoG electrodes for human use are commonly made of platinum, platinum-iridium, stainless steel, or silver, and embedded into a thin flexible silastic sheet. The diameter of conventional clinical electrodes is typically 4 mm, with 2.3 mm of the contact exposed, and the interelectrode distance is usually 10 mm from center to center (see Figure 16.2). Electrode arrays can be arranged in square, rectangular,
or L-shaped configurations. In the United States, the implantation duration is limited by the U.S. Food and Drug Administration (FDA) to a maximum of 28 days, and the typical implant duration is about 1 week. All relevant implant parameters (duration of the implant and size of the craniotomy) are determined solely by the clinical needs of the patients and without any regard for research interests.

After the implantation of the electrodes, bioamplifiers with high temporal resolution (i.e., an adequate sampling rate) and with sufficient range and resolution in voltage (i.e., an adequate quantization level) are required to capture all important features of ECoG signals. In practice, a sampling rate of 1 kHz or higher, a voltage range of at least several dozens of µV, and a digital resolution of 24 bits are recommended. These are good recording practices, as the spectral bandwidth of ECoG signals extends to ~250 Hz, and voltage amplitudes attenuate inversely with increasing frequency (i.e., from several hundred microvolts at low frequencies to several hundred nanovolts at higher frequencies). Ideally, the bioamplifier should minimize the amount of analog filtering: high-pass filters can remove evoked potentials of interest, whereas low-pass filters with too low of a cutoff frequency will remove important high-frequency content of ECoG signals. The physiological basis of these signals and the most relevant features for BCI applications are discussed in Section 16.3.

16.3 ECoG SIGNAL PHYSIOLOGY

Macroscale field potentials are generated by current dipoles between cortical laminae (Nunez and Srinivasan 2006). The physiological underpinnings of the current source density (CSD) in cortical laminae that give rise to these potentials were established experimentally in the late 1970s and early 1980s (Mitzdorf 1985). These studies demonstrated that propagating action potentials in axons and axonal terminals do not contribute strongly to the CSD at spatial scales of ~50–300 µm or greater, which suggests that ECoG signals comprise dendritic synaptic current exchange (i.e., influx and efflux) that modulates the CSD. This has recently been substantiated by simultaneous in vivo recordings of the intracellular potential and local field potentials over which ECoG signals are averaged, showing tight temporal coupling that is independent of the spiking pattern of the neuron (Miller 2010; Miller et al. 2009a; Okun et al. 2009). Thus, ECoG signals can be explained by synchronous synaptic inputs from large ensembles underlying the electrode. If this synchronization/desynchronization occurs rhythmically, it can be observed as rhythmic amplitude modulations in the time series (Figure 16.3a) and as a peak in the frequency domain (Figure 16.3b) (Ritaccio et al. 2011). If the synchronization is related to a stimulus (e.g., a visual cue) or an event (e.g., movement onset), the time series may reflect a multiphasic, time-locked response, known as an “event-related potential” (ERP).

In addition to ERPs, whose physiological origin is complex and unresolved (Kam et al. 2016; Makeig et al. 2002; Mazaheri and Jensen 2006, 2008), ECoG signals also contain two components that are particularly relevant to BCIs: broadband gamma and low-frequency oscillations. ECoG broadband gamma activity (often measured in the 70–170 Hz range) has been suggested by many studies to be the key indicator of cortical population-level activity (Aoki et al. 1999; Canolty et al. 2007; Chang et al. 2011; Crone et al. 2001a,b, 1998a; Darvas et al. 2010; Edwards et al. 2010, 2005, 2009; Freeman et al. 2000; Jensen et al. 2007; Kubánek et al. 2009; Lachaux et al. 2007; Leuthardt et al. 2007, 2004; Maris et al. 2011; Menon et al. 1996; Miller et al. 2007, 2010b; Pei et al. 2010; Pfurtscheller et al. 2003; Ray et al. 2008; Sanchez et al. 2008; Schalk et al. 2007; Sinai et al. 2005; Tort et al. 2008; Voytek et al. 2010; Wang et al. 2010). Broadband gamma has been shown to be a direct reflection of the level of cortical excitation, that is, a reflection of the average firing rate of neurons directly underneath the electrode (Manning et al. 2009; Miller et al. 2009b; Ray and Maunsell 2011; Whittingstall and Logothetis 2009), and has been shown to drive the BOLD signal identified using fMRI (Lachaux et al. 2007; Engell et al. 2012; Logothetis et al. 2001; Mukamel et al. 2005; Niessing et al. 2005). Thus, the use of broadband gamma (which is not readily available in scalp-recorded EEG) provides a link between ECoG-based research and work using single-neuron recordings and fMRI. Broadband gamma activity usually presents itself as a broad spectral distribution above 60 Hz that follows a 1/f trend in the frequency domain (Miller et al. 2009a,c). Most relevant to BCI development, many studies have reported that topographically
focused broadband gamma activity correlates closely with specific aspects of behavior such as the direction of limb movements (Kubánek et al. 2009; Leuthardt et al. 2004; Schalk et al. 2007; Miller et al. 2009c; Acharya et al. 2010; Gunduz et al. 2016; Pistohl et al. 2008; Wang et al. 2012) (see Figure 16.4).

In contrast to broadband gamma, low-frequency oscillatory activity provides an index of cortical excitability (Fitzgibbon et al. 2004; Haegens et al. 2011; Howard et al. 2003; Kubanek et al. 2015, 2013; Miltner et al. 1999; Sederberg et al. 2003; Singer and Gray 1995; Szczepanski et al. 2014; Womelsdorf et al. 2006) and plays a central role in the dynamic modulation of cortical function in response to varying task demands (Fries 2005; Jensen and Mazaheri 2010; Schalk 2015). Thus, even though low-frequency activity is likely produced by electrical events in certain (putatively subcortical) populations of neurons, it has proven to be a useful metric of the modulation of the cortex that is different from cortical excitation indexed by broadband gamma. Oscillations at different frequencies subserve different cortical regions. For example, activity in the alpha (8–12 Hz) band is prevalent throughout the sensorimotor system (e.g., Kubanek et al. 2015, 2013) where it is usually referred to as the mu rhythm that is well described in the classical EEG literature (Chatrian 1976) (see Figure 16.5 Brunner et al. 2009). Typically, the mu rhythm and the closely associated beta (18–26 Hz) rhythm are relatively focused spectrally and appear as peaks in the power spectrum but are relatively widespread spatially (see Figure 16.5a, bottom). Although their peak amplitude modulates with actual or imagined movements (Crone et al. 1998b; Pfurtscheller and Cooper 1975) (see Figure 16.6 Schalk 2006), activity in mu or beta bands appears to reveal only modest information about localized differential cortical processing (Toro et al. 1994). Outside the sensorimotor system, alpha oscillations are also prevalent in the visual system (e.g., Van Dijk et al. 2008) and auditory system (e.g., Potes et al. 2014, 2012). In contrast, oscillations in the theta (4–8 Hz) band are pervasive in prefrontal and hippocampal networks (Anderson et al. 2009; Dürschmid et al. 2014; Fujisawa and Buzsáki 2011). Across all these types of systems and oscillations, oscillatory amplitude is typically large during rest, and reduced while the subject is engaging in corresponding function (e.g., Figure 16.6).

FIGURE 16.5  Example of ECoG during the task of repetitively opening and closing the hand and during rest. (a) Signals in the mu/beta band (5–30 Hz) decrease with the task and are spatially less specific (i.e., they are broadly distributed topographically), whereas signals in the gamma band (i.e., 70–116 Hz as measured here) increase with the task and are spatially more specific (i.e., they are sharply focused topographically). (b) The power spectrum on a logarithmic scale for the electrode marked with a star in the topographies illustrates the decrease in the mu/beta band (marked by the green bar) and increase in the gamma band (orange bar). (From P. Brunner, A. L. Ritaccio, T. M. Lynch, J. F. Emrich, J. A. Wilson, J. C. Williams, E. J. Aarnoutse, N. F. Ramsey, E. C. Leuthardt, H. Bischof, and G. Schalk. A practical procedure for real-time functional mapping of eloquent cortex using electrocorticographic signals in humans. Epilepsy Behav, 15(3):278–286, Apr 2009.)
Cortical excitability and cortical excitation (as measured by oscillatory and broadband gamma activity, respectively) are intrinsically linked: cortical activity is usually highest during periods when oscillatory power is low or when oscillations are in their trough. The latter relationship between the phase of low-frequency oscillations and the amplitude envelope of the signal in the broadband gamma range is usually referred to as phase–amplitude coupling (PAC; see Figure 16.7 Schalk and Leuthardt 2011) (Canolty et al. 2006). Recent research has increasingly pointed to a link between changes in PAC and different neurological or psychiatric disorders (Allen et al. 2011; Crowell et al. 2012; de Hemptinne et al. 2013; Shute et al. 2015; Uhlhaas and Mishara 2007; Uhlhaas and Singer 2010).

FIGURE 16.6  Example of ECoG signals during a task and rest. (a) Raw ECoG signals from one subject during rest (black trace) and while imagining saying the word “move” (red trace). The amplitude of the oscillation associated with rest decreases with imagery. (b) Frequency spectra for the corresponding conditions. Imagery is associated with decrease in the mu (8–12 Hz) and beta (18–26 Hz) frequency bands. (From G. Schalk. Towards a Clinically Practical Brain–Computer Interface. PhD thesis, Rensselaer Polytechnic Institute, Troy, Dec 2006.)

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In addition to ECoG potentials that are evoked by discrete motor movements or sensory stimuli, and to oscillatory and broadband activity, recent studies (Kubánek et al. 2009; Schalk et al. 2007; Acharya et al. 2010; Gunduz et al. 2016; Pistohl et al. 2008) describe a continuous time-domain ECoG feature called the local motor potential (LMP) that encodes different aspects of movements. LMPs are observed mainly in the prefrontal cortex (Schalk et al. 2007; Gunduz et al. 2016). The physiological origin of the LMP remains unknown and its potential value for ECoG-based BCIs has not been explored beyond these studies.

Because of its closer proximity to the neurons producing electrical modulations, ECoG has larger signal amplitude and broader bandwidth compared to EEG. In addition to these advantages of signal quality, ECoG electrodes may provide greater long-term functional stability (Bullara et al. 1979; Loeb et al. 1977; Margalit et al. 2003; Pilcher and Rusyniak 1993; Yuen et al. 1987) than intracortical electrodes, which induce tissue responses that may degrade or prevent neuronal recordings. A study by Chao et al. (2010) in primates showed that the signal-to-noise ratio of ECoG signals and the BCI features of motor function are stable over several months (Schalk 2010). Thus, there is strong support that ECoG-based BCIs provide high functional specificity and are less susceptible to the problems of reliability and long-term stability that often affect other electrophysiological signal-acquisition methodologies.

16.4 CURRENT ECoG-BASED BCIs

16.4.1 ECoG BCIs for Control

BCI systems based on ECoG have advanced well beyond initial proof of concept. As of 5 years ago, ECoG BCIs had been extensively validated across numerous different labs (Leuthardt et al. 2004, 2006; Miller et al. 2007; Blakely et al. 2009; Brunner et al. 2011; Felton et al. 2007; Hinterberger et al. 2008; Rouse and Moran 2009; Schalk 2008; Vansteensel et al. 2010; Wilson et al. 2006). In the first paper reporting an ECoG BCI with humans (Leuthardt et al. 2004), four participants could move a cursor up or down by performing or imagining different movements. Overall, the four subjects attained 74%–100% accuracy (with 50% chance accuracy) in the task of moving the cursor to a target on the top or bottom of the monitor. This real-time control required only 3–24 min of training (see Figure 16.8a for learning curves). This performance is difficult to compare to BCIs based on EEG because of the limited amount of data from only four subjects, but the training required for such control does appear to be shorter than that for EEG-based BCIs based on motor imagery (see Figure 16.8a). The authors also conducted offline analyses of data from all four subjects while they moved a cursor in two dimensions using a joystick. Their results showed that ECoG features as high as 180 Hz encoded movement direction (see also Figure 16.4a).

Subsequent work included several improvements that extended this study beyond one-dimensional control. Schalk et al. (Schalk et al. 2008) presented a BCI that allowed five subjects to control two-dimensional movement in real time based on ECoG measures of imagined or actual movements. A more recent study presented offline decoding of three-dimensional movements in humans (Bundy et al. 2016). Actual two- and three-dimensional control was shown in a patient with tetraplegia resulting from a C4 spinal injury (Wang et al. 2013). This was the first publication that reported real-time ECoG-based robotic arm control in a tetraplegic patient (see Section 16.5). Despite this successful demonstration of improved control, the ECoG array had to be explanted within 28 days of implantation to comply with requirements from the FDA. In a different direction based on ipsilateral ECoG activity from four chronic stroke patients with severe paralysis, Spueler et al. successfully discriminated seven distinct hand movement intentions (Spueler et al. 2014). This research direction could go beyond high-dimensional control to allow more natural control based on hand movement imagination.

While improving the number of dimensions of movement is important, other work has instead focused on making ECoG BCIs more flexible by supporting control from other brain regions. Two studies (Yuen et al. 1987; Wilson et al. 2006) conducted research based on ECoG activity that reflected sensory (not motor) function, with an electrode spacing of about 5 (not 10) mm, resulting in
control that was roughly comparable to Ref. (Leuthardt et al. 2004). Related work showed that primates could learn to control one-dimensional cursor movement via broadband gamma hand activity by modulating activity of any ECoG electrode in motor or premotor areas (Rouse and Moran 2009), further extending the potential flexibility of ECoG BCIs. Slightly later research showed that humans can quickly learn to direct movement through ECoG activity from the left dorsolateral prefrontal cortex, associated with working arithmetic memory (Vansteensel et al. 2010). Collectively, these studies suggest that patients could attain control from a wide variety of ECoG locations while performing tasks beyond motor control.

Human ECoG BCIs were shown to provide a stable signal across 5 days of recording (Blakely et al. 2009). Slightly later work showed that motor imagery BCIs produced more pronounced changes in ECoG activity over the motor cortex than actual movements (Miller et al. 2010).

Collectively, these results from ECoG BCI research with humans and primates have provided the motivation and potential for improved systems that could use a variety of options for electrode positions and associated mental tasks. For the minority of BCIs that do require significant training (typically based on motor imagery), ECoG BCIs should entail less training and provide improved control. The improved spatial resolution (and in particular the use of broadband gamma that is not readily detectable in EEG recordings) should provide the foundation for new directions with ECoG BCIs for control, as well as other goals such as communication that is addressed in Section 16.4.2.

16.4.2 ECoG BCIs for Communication

During early BCI research, most work was focused on providing communication for severely disabled users through BCI paradigms involving visual attention or imagined movements (Wolpaw et al. 2002). One common approach used the P300 and other EEG activity associated with voluntary
selective attention to spell or select other items from a matrix of choices, and this paradigm is still widely employed (Fazel-Rezai et al. 2012; Powers et al. 2015). In 2011, the first matrix speller using ECoG was reported (Brunner et al. 2011). One subject with ECoG electrodes implanted in the occipital lobe used P300 and visual evoked potentials to spell very effectively, attaining 17 characters/min (69 bits/min) over sustained BCI operation and 22 characters/min (113 bits/min) at peak. These rates are considerably higher than those reported for EEG-based P300 spellers at that time and are still higher than typical EEG-based P300 BCIs today. Two additional studies also achieved encouraging results with a similar approach (Krusienski and Shih 2011a, b). Another study (Krusienski and Shih 2011c) defined the spectral components involved in such ECoG-based BCIs.

Other groups have explored paradigms to select characters and/or other items using ECoG measures of motor imagery. For example, Hinterberger et al. (2008) presented a two-class ECoG BCI based on imagination of either tongue or hand movement. Using these two commands, participants could select characters through a sequence of binary selections. The subject with the best performance required about 3 min to convey one character.

A more recent study provided communication for a patient with amyotrophic lateral sclerosis (Vansteensel et al. 2016). The study utilized a fully implanted ECoG-based BCI device (Activa PC+S, Medtronic, Minneapolis, Minnesota (Afshar et al. 2012; Rouse et al. 2011; Stanslaski et al. 2012)) with subdural ECoG electrodes over cortical motor areas and a subcutaneously placed transmitter in the thorax. The patient could convey about two letters per minute by imagining hand movement. The patient also used the BCI with their eye-tracking system, both simultaneously and as an alternate communication tool (see Section 16.5). The BCI provided communication through an implanted device designed for chronic recording and remained effective 28 weeks after electrode placement. This study showed that an ECoG BCI can provide practical communication, even in a hybrid environment with an eye-tracker, for about 7 months after implantation surgery.

In addition to working with selective attention and imagined movement, several ECoG studies have introduced communication options that may not be readily viable with EEG BCIs or any current noninvasive imaging method. For example, ECoG signals may be employed to decode phonemes or words that a subject speaks or even simply imagines (Pei et al. 2010, 2011; Kellis et al. 2010; Leuthardt et al. 2011; Martin et al. 2016; Mugler et al. 2015, 2014). These approaches generally rely on ECoG electrodes placed on the temporal lobe since this region includes Wernicke’s area and earlier auditory processing areas over superior temporal gyrus. ECoG activity reflecting speech processing has also been explored over Broca’s area and nearby motor areas involved in speech. One study used ECoG to explore vocal track kinematics as six participants articulated nine vowels. The authors could predict lip kinematics based on ECoG activity from ventral sensorimotor cortical areas (Bouchard et al. 2016). Advancing beyond isolated phonemes or words, Brumberg et al. (Brumberg et al. 2016) explored ongoing spatiotemporal changes in cortical activity while people overtly or covertly read sentences continuously, and Martin et al. (2014) and Herff et al. (2015) decoded complete spectrotemporal representations and even whole sentences from ECoG, respectively. Another study explored ECoG activity while 10 patients listened to a rock song or spoken narrative (Sturm et al. 2014). The authors could precisely and reliably identify the moments when spoken lyrics began and ended within the rock song, and showed that broadband gamma power over temporal areas reflected processing dynamics relating to different aspects of sound such as pitch and timbre. These new approaches could lead to BCIs based on words, sentences, or other speech-related activity that people simply imagine. BCIs that can directly interpret imagined words, sentences, or related mental activities could lead to major advances for BCIs in terms of ease of use, practicality, flexibility, bandwidth, and other factors.

### 16.4.3 ECoG BCIs for Neuromodulation

Over the past several years, human and animal neurophysiologists have begun to increasingly explore ECoG to explain neurophysiological correlates of disease. Intraoperative studies during deep brain stimulation (DBS) electrode implantation surgeries (during which the patients remain...
awake) provide a particularly opportune window for these studies. Acute intraoperative ECoG strips can be implanted during these surgeries to study thalamocortical or basal ganglia–cortical pathways of disease. Many studies in the literature point to pathologically high beta band activity in the basal ganglia–cortical network in Parkinson’s disease (PD) (Bronte-Stewart et al. 2009; Brown et al. 2001; Levy et al. 2002). Moreover, the amplitude of the beta rhythm correlates with clinical measures of symptom severity in PD (Bronte-Stewart et al. 2009; Brown et al. 2001; Levy et al. 2002). In a similar intraoperative study of essential tremor (ET), which consists mostly of slow tremors (4–8 Hz) of the upper extremities, Air et al. (2012) reported high coherence with the primary motor cortex ECoG activity and an accelerometer placed on the tremor dominated hands of patients. Studying the neural correlates of neurological disorders not only contributes to our understanding of the pathophysiologies, but may also allow us to develop better treatment strategies.

DBS, which has been an FDA-approved treatment for PD and ET since the early 1990s (Okun 2014a), aims to suppress pathophysiological activity that leads to symptoms by delivering electrical pulses to target deep-brain structures (such as the basal ganglia nuclei or thalamic subregions). The clinical personnel that program the stimulation settings (amplitude, frequency, and pulse width of the electrical current), however, do not necessarily have a scientific understanding of the underlying pathology or the physiological response to the adjustments to various stimulation parameters. Instead, they base their decisions on the observable behavioral responses and verbal response of patients. This is known as an open-loop DBS system. Studying the neurophysiological signatures of neurological disorders and the after-effects of brain stimulation would enable direct interpretation of the disorder and provide insight into treatment options that can be tailored to the current clinical condition of the patient. A DBS system that responsively stimulates when pathological signals are present or adaptively modifies stimulation parameters to match the degree of pathology is called a closed-loop DBS system. Although the clinical value of a DBS system that can initiate stimulation and/or adapt its stimulation parameters to the input received from the brain signals has long been recognized within the neuromodulation community (McIntyre 2015), the proof of concept has been lacking and the clinical efficacy of closed-loop DBS remains to be demonstrated in movement disorders.

One of the barriers to this goal has been the fact that these studies were thus far limited to the operating rooms. Recently, next generation bidirectional devices capable of performing chronic brain recordings in humans have emerged, and we present examples of these systems in Section 16.5. These devices allow for studying and tracking of the pathophysiological neural signals that can drive therapeutic stimulation. However, tracking a neuromarker on the electrode array used for stimulation is usually challenging in these implantable devices owing to amplifier saturation or significant stimulation artifacts. Thus, many groups are now seeking FDA investigational device exemption (IDE) to implant an ECoG strip from which they can extract the pathophysiological neuromarker and deliver stimulation to deep brain structures. The ECoG strip is far enough from the cortically implanted electrodes and is not significantly affected by the stimulation artifact because of this distance and the much higher signal amplitudes in ECoG. For instance, the pathological beta rhythms in PD that are present in the basal ganglia are also present in motor cortex and thus can be used as a marker to drive closed-loop DBS (Little et al. 2013; Rosa et al. 2015).

Moreover, an additional ECoG strip allows researchers to study basal ganglia–cortical networks or thalamocortical networks of disease in humans when stimulation is temporarily turned off. Shute et al. (2015) studied the thalamocortical network of Tourette syndrome (TS) with Activa PC+S devices. TS is a highly complex neuropsychiatric disorder characterized by involuntary motor and vocal tics. Figure 16.9 shows data recorded chronically in two patients with TS with bilateral implants in the centromedian-parafascicular (Cm-Pf) complex of the thalamus, which is the most common DBS target for TS, and bilateral ECoG strips over their hand motor cortices. Figure 16.9 shows the differences in signal modulations during involuntary hand motor tics and voluntary hand movements. During both types of movement, beta desynchronization is evident in motor cortex. Only during involuntary tics is there a deviation from the baseline in the raw Cm-Pf recordings that is reflected as increase in the low-frequency activity in the spectrogram.
In addition to studying disease biomarkers, bidirectional neural implants could enable studying the neural correlates of DBS therapy and could uncover how DBS modulates neural networks to bring about symptom relief. As discussed above, recent evidence supports the argument that local neuronal population activity, as detected via broadband gamma amplitude shifts, is co-modulated with the phase of lower frequencies (Voytek et al. 2010; Canolty et al. 2006; Miller et al. 2010). In an intraoperative study, de Hemptinne et al. (2013) showed pathologically high coupling between beta phase-broadband gamma in the motor cortex of PD patients compared to epilepsy and dystonia patients. The signals as captured through ECoG strip electrodes placed over the hand motor cortex intraoperatively (see Figure 16.10). The same group recently also showed that optimal DBS stimulation that brought symptom relief also decreased this coupling (see Figure 16.11) (de Hemptinne et al. 2015). In a similar study in TS, Shute et al. showed that there was no significant coupling in the motor cortices of TS patients and that optimal DBS increased this coupling (see Figure 16.12 Okun 2014b). These results are interesting, as they provide an ECoG biomarker that is exaggerated for a hypokinetic disorder (PD) and is absent for a hyperkinetic disorder (TS). Moreover, through ECoG, these studies present how DBS brings these patients to a healthier, less symptomatic state through stimulation of different nodes in the motor network. This ECoG biomarker can be used to adaptively change DBS parameters in both disorders and to develop adaptive closed-loop DBS systems in the future.


FIGURE 16.12  Representative example of coupling observed in motor cortex of a Tourette syndrome patient before (left), during (middle), and after Cm-Pf stimulation (right). (From M. Okun. Tourette syndrome deep brain stimulation, clinicaltrials.gov identifier:nct02056873. https://clinicaltrials.gov/ct2/show/NCT02056873, 2014.)
16.5 CURRENT IMPLANTABLE DEVICES

Recent years have seen an increase in the development, testing, and regulatory approval of implantable recording and stimulation systems for BCI use. We introduced the Activa PC+S system (Afshar et al. 2012; Rouse et al. 2011; Stanslaski et al. 2012) in Section 16.4. The system has received FDA IDE; however, clinical investigations are currently clinician initiated with a right of reference from Medtronic. The Activa PC+S is the same form factor and has the equivalent capability as the commercially available Activa PC, which connects to two four-contact electrode arrays (commonly referred to as leads by DBS clinicians) for stimulation delivery. The device is implanted in the chest cavity, similar to a pacemaker. In addition to providing predicate therapy capabilities, the Activa PC+S adds key elements to facilitate chronic research, such as two channels of ECoG or LFP amplification and spectral analysis, algorithm processing, event-based data logging, and wireless telemetry for data uploads and algorithm/configuration updates (Rouse et al. 2011). The device is capable of recording time-domain brain signals from one bipolar electrode configuration from each lead simultaneously at sampling rates of 200, 422, or 800 Hz (Rouse et al. 2011). It can also record the desired spectral power of a frequency band in four channels at 5 Hz (Rouse et al. 2011). Data can be streamed to a computer for algorithm development (Afshar et al. 2012), or an embedded linear discriminant analysis classifier can be used to detect events (Stanslaski et al. 2012). Figure 16.13 shows the schematic presented in the Vansteensel et al. study with a locked-in patient (Vansteensel et al. 2016). Data are streamed out to control a speller. If a study involves stimulation (which is not the case in Figure 16.13), stimulation parameters are set using a separate clinical stimulation programmer. The patient receives a programmer to switch between open- and closed-loop settings and an event marker, which triggers a recording. A second-generation rechargeable device with higher channel counts and better stimulation artifact rejection, the Activa RC+S, is currently being developed (Bourget et al. 2015). These two devices are registered with the BRAIN Initiative Public-Private Partnership Program.

A system that has received approval from the FDA is the NeuroPace (Mountain View, California) Responsive Neurostimulator (RNS) for the treatment of intractable epilepsy (Morrel and RNS System in Epilepsy Study Group 2011). The RNS System provides responsive cortical stimulation via a cranially implanted programmable neurostimulator connected to one or two recording and stimulating four-contact depth or subdural cortical strip leads that are surgically placed in the brain according to the seizure focus (see Figure 16.14 Heck et al. 2014). The neurostimulator continually senses ECoG or LFP activity and is programmed by the physician to detect abnormal neural activity and then provide stimulation. The physician adjusts detection and stimulation parameters for each patient to optimize control of seizures. The device is fully implanted in the skull (see Figure 16.14). Other components include a physician programmer, a patient remote monitor and a magnet for marking events. A multicenter, double-blind, randomized controlled trial assessing the safety and effectiveness of responsive cortical stimulation study as an adjunct therapy for partial onset seizures was conducted in 191 adults with medically refractory epilepsy. The study is registered on ClinicalTrials.gov (NCT00264810), and the results of the study are publically available. The RNS system is registered with the BRAIN Initiative Public-Private Partnership Program.

The French WIMAGINE system is capable of real-time recording and wireless transmission of the ECoG signals from 64 electrodes at a sampling rate of 600 Hz to an external computer housing the control software (see Figure 16.15) (Mestais et al. 2015). The hermetic housing and the antennae have been designed and optimized to ease the surgical implantation in the skull. The software system is designed for BCI use.

The Australian NeuroVista device was an implantable seizure advisory system for patients with intractable epilepsy. Two silicon implantable lead assemblies, each with eight platinum iridium contacts distributed across two electrode arrays, collect ECoG at a sampling rate of 400 Hz (Cook et al. 2013) and the system wirelessly transmits these data to an external, handheld personal advisory
device (see Figure 16.16). The implantable telemetry unit is inductively recharged through an external charging accessory. A terminated clinical trial for safety and efficacy with 15 patients is registered with ClinicalTrials.gov (NCT01043406).

The German BrainInterchange system by CorTec (see Figure 16.17) is based on a fully implantable device for recording and stimulation in humans. It provides 32 electrode contacts, all of which can be used for signal recording (1 kHz sampling rate at 16 bit dynamic range) or brain stimulation (maximum 6 mA/2.5 ms). The system consists of (a) the electrodes; (b) a hermetically encapsulated...
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An electronic unit that amplifies, digitizes, and broadcasts brain signals and directs electrical stimuli to selected electrodes; (c) a telemetric unit that is placed outside the body on the skin; and (d) a wearable controller unit. The telemetric unit communicates with the implant and provides it wirelessly with energy. The controller unit (laptop PC) runs a software interface to custom-specific application software. The application software that controls the brain signal data stream, analyzes the data, takes decisions, and sends commands to the implant that can be customized for a specific application by the user in C++, Python II, or MATLAB.


16.6 OPEN QUESTIONS AND DIRECTIONS FOR FURTHER RESEARCH

At present, most ECoG-based BCI research is still performed in human subjects who have been temporarily implanted with an ECoG array for the purpose of presurgical assessments. Thus, substantial practical constraints and challenges affect the design of ECoG-based BCI studies. Perhaps the most hindering issue is the limited amount of time that is available with these subjects. This may be the main reason that there are still relatively few online human ECoG-based BCI studies in the
literature today (Leuthardt et al. 2004, 2006; Miller et al. 2010b; Blakely et al. 2009; Brunner et al. 2011; Felton et al. 2007; Hinterberger et al. 2008; Rouse and Moran 2009; Schalk 2008; Vansteensel et al. 2010; Wilson et al. 2006; Wang et al. 2013). At the same time, together with the many offline BCI-related studies, this work strongly encourages further investigations of ECoG BCI technology.

Another limitation of ECoG studies performed with this patient population is the electrode size and interelectrode distance of the clinical arrays that are currently being used. As discussed in previous subsections, conventional clinical grids are often configured as an 8-by-8 array with 1 cm interelectrode spacing and an exposed contact diameter of 2–3 mm. These arrays are designed with such large contact area surfaces to yield low impedance values (around several hundred ohms), which prove to be advantageous in the noisy environment of a hospital room. A grid can spatially cover a large area of a lateral hemisphere but samples sparsely because of the large interelectrode distance, typically from only a few electrodes on a given gyrus (Chang 2015). The optimal electrode size and interelectrode distance to maximize the amount of information extracted through ECoG is one of the most important open questions in the field. While smaller electrodes, sometimes referred to as micro-ECoG, can bring about improved spatial selectivity, this comes at the expense of increased impedance. Moreover, while more channels may promise increased spatial sampling, an increased number of channels provides practical and clinical challenges. Some studies have utilized micro-ECoG arrays to show higher information extraction in the superior temporal gyrus to study speech generation (Bouchard et al. 2016; Chang et al. 2010; Mesgarani et al. 2014) and to show improved BCI performance (Kellis et al. 2010, 2016; Leuthardt et al. 2009). A computational finite element modeling study that predicted the biophysical correlation between electrodes at various distances suggested a minimum spacing of 1.7–1.8 mm for subdural recordings (Slutzky et al. 2010), which is still larger than the size of cortical ocular dominance columns in the human visual cortex that are about 1 mm wide (Adam and Horton 2008). It should be noted that correlation between electrode recordings, and thus optimal electrode spacing, is dependent on frequency. As discussed earlier, lower frequencies are more broadly distributed while high frequencies are spatially more focal. Thus, it is not surprising that when Chang (2015) computed the correlation of different spectral bands as a function of electrode distance, correlation was lowest for the broadband gamma band at the lowest electrode spacing and higher for lower frequencies (see Figure 16.18).

FIGURE 16.18 Human cortical recordings obtained on a 4-mm-spaced ECoG grid. Significant differences in spatial resolution, especially at less than 1 cm, can be observed depending on the frequency band of interest. Correlations for distances less than 4 mm are extrapolated. (From E. F. Chang. Towards large-scale, human-based, mesoscopic neurotechnologies. Neuron, 86(1):68–78, Apr. 2015.)
Rouse et al. (Rouse et al. 2016) utilized micro-ECoG electrodes with 300 μm diameter for one-dimensional and two-dimensional BCI tasks in primates. They tested the effect of interelectrode distance on BCI control between 3 and 15 mm. The primates achieved successful BCI control with two electrodes separated by 9 and 15 mm. Performance decreased and the signals became more correlated when the electrodes were only 3 mm apart. Overall, more systematic studies informed by computational models are imperative to determine the optimal electrode design for BCI utility.

It should be noted that in the study by Rouse et al. (2016), the electrode arrays were placed epidurally, that is, on top of the dura, which does not require a dural incision. Given that most complications involved in epilepsy surgery are related to infections due to incisions to the dura (Van Gompel et al. 2008), studying the signal fidelity of epidural ECoG could lead to a potentially less invasive BCI system and a justification for BCI users to undergo implantation of such systems with benefits potentially outweighing the risks. For instance, Spueler et al. (2014) temporally implanted ECoG strips epidurally in chronic stroke patients with paresis. In this study, the authors were able to decode seven imagined hand movements from the ipsilateral hemisphere. In another study, Bundy et al. (2014) utilized simultaneously acquired epidural and subdural ECoG signals while the patients were at rest. Both macro-scale (2-mm-diameter electrodes with 1-cm interelectrode distance, one patient) and micro-scale (75-μm-diameter electrodes with 1-mm interelectrode distance, four patients) ECoG electrodes were tested. While subdural micro-ECoG contacts have significantly higher spectral amplitudes and reached the noise floor around 150–200 Hz, epidural micro-ECoG contacts reached the noise floor around 80 Hz. Epidural placement of macroelectrode grids did not affect the noise floor significantly. More studies are needed to confirm these results in behaviorally modulated signals and BCI tasks.

### 16.7 SUMMARY

With its unique characteristics, ECoG is producing strong support and growing excitement for its potential as a BCI signal modality. ECoG is likely to be an integral part of foreseeable chronic neural implants because of its high signal fidelity, long-term stability, and relatively low demands on sampling rate, thus greatly reducing the power requirements of the implantable system.

Using similar signal-processing techniques, ECoG BCIs can make use of similar features used in EEG-based BCIs, mainly the mu and beta rhythm bands prominent in the scalp-recorded EEG over sensorimotor cortex. In addition, it also yields higher-frequency broadband gamma activity and, with depth electrodes, activity from subcortical structures that cannot be captured over the scalp. ECoG high-frequency activity reflects asynchronous synaptic activity, demonstrates greater functional localization than the low-frequency synchronized rhythms, and thus may be particularly beneficial to improve the performance of a BCI system. In addition, ECoG also detects the LMP, which has been shown to have a differential role in decoding motor execution and planning.

ECoG-based BCI studies to date have been limited primarily to people temporarily implanted with ECoG recording arrays before epilepsy surgery. However, with increased interest and investment in implantable technologies, ECoG arrays are being implanted chronically and in various disease conditions. In this case, it can provide an interface to stably record from and stimulate both cortical and subcortical neuronal populations. Thus, compared to scalp-recorded EEG, its use should enable an array of new neuromodulation applications. At the same time, to maximize the benefit and the utility of ECoG, the following open questions need to be addressed: can signal acquisition be improved through optimal electrode design or optimal electrode placement; can epidural ECoG yield acceptable BCI performance? Also, can BCI performance be improved by optimizing feature selection or through a combination of features (such as broadband gamma and LMP)? These questions should keep the field active and vibrant for the decade ahead.

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