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Technological Approaches to the Scientific Explorations of Epilepsy and Behavior

Proceedings of the First International Workshop on Advances in Electrocorticography

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ABSTRACT

In October 2009, a group of neurologists, neurosurgeons, computational neuroscientists, and engineers congregated to present novel developments transforming human electrocorticography (ECoG) beyond its established relevance in clinical epileptology. The contents of the proceedings advanced the role of ECoG in seizure detection and prediction, neurobehavioral research, functional mapping, and brain–computer interface technology. The meeting established the foundation for future work on the methodology and application of surface brain recordings.

1. Introduction

1.1. Anthony Ritaccio, Gerwin Schalk

On October 2009, the First International Workshop on Advances in Electrocorticography (ECoG) was held in Bolton Landing, NY, USA. The purpose of this international workshop was to gather experts from various disciplines who are currently redefining the methods and capabilities of ECoG recordings in humans.

Historically, the first electrical recordings of the human brain by Hans Berger were on a patient with a recently trephined skull, an "electrodurogram" rather than literal ECoG [1]. For most of its practical application from the late 1930s through the past decade, the main use of ECoG has been in the domain of epilepsy for the localization of epileptogenic brain tissue. By the mid-1980s, many U.S. epilepsy centers had abandoned the "classic" form of intraoperative interictal ECoG to guide cortical excision [2]. The main utility of direct recordings from the cortical surface has largely remained unchanged to the present day, finding its main expression in chronic recordings for visual inspection via subdural grids and strips in specialized epilepsy monitoring units for the analysis of interictal and ictal events to assist surgical planning.

Recent developments, however, are rapidly transforming human ECoG into a vibrant recording technique with relevance far beyond the field of clinical epileptology. Advancements in digital electroencephalography (EEG) technology have allowed wide expansion in spatial and temporal sampling. This has led to the appreciation of high-frequency oscillations [3] and their relationship to epileptic tissue as well as demonstrations of task-related gamma (40–200 Hz) activity changes, the topographic and temporal patterns of which are consistent with the functional anatomy and processing dynamics of sensorimotor, auditory, visual, and language function [4]. Simultaneously, computational neuroscientists and engineers have found the fidelity and robustness of ECoG signals to be a promising modality for pioneering work in brain–computer interface (BCI) technology [5,6].

The unique confluence of these innovations has vital implications for widely varied applications including seizure prediction, neurobehavioral research, ECoG-based functional mapping, and BCI-driven neuroprosthetics. These applications, along with the methodologies and technologies that facilitate them, were the subjects of our timely symposium, the proceedings of which are offered below.

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2. History and basics of electrocorticography recordings

2.1. Nathan E. Crone, Mackenzie C. Cervenka

Surgical implantation of intracranial electrodes remains an important option for patients with intractable epilepsy in whom the ictal focus cannot be reliably localized with noninvasive methods and/or is perilously close to functionally important brain structures. In these circumstances, it is necessary to localize cortical function at a spatial resolution that is comparable to that of ictal localization and that can be used to tailor the surgical resection. Throughout the entire history of epilepsy surgery, the chief technique for mapping brain function in these circumstances has been electrocortical stimulation mapping (ESM). Although this has been a very effective tool for both intraoperative and extraoperative functional mapping and has also been widely used to investigate the neural correlates of human brain function, cortical stimulation often elicits epileptiform afterdischarges, which can sometimes evolve into seizures. This can delay or prevent functional mapping at some sites, particularly those closest to the seizure focus, and medications given to prevent afterdischarges can interfere with recording seizures for ictal localization. Additionally, electrical stimulation can elicit pain, presumably through trigeminal afferents in blood vessels, also preventing mapping of essential sites. Finally, ESM must be performed sequentially at pairs of electrodes, preferably finding the optimal stimulus intensity at each pair. This can be time consuming, particularly if a battery of functional tasks are tested at every stimulation site. These limitations have motivated clinicians to explore the possibility of mapping brain function using passive ECoG recordings that are already being obtained continuously in these patients to capture seizures.

Electrocorticographic signals can be recorded during batteries of the same or similar tasks used for ESM and can be analyzed offline or in real time to distinguish task-related activity from resting/baseline activity. Although phase-locked components of ECoG responses (i.e., evoked and event-related potentials) were initially emphasized, recent studies have also appreciated task-induced changes in ongoing cerebral activity that are not necessarily phase locked to a stimulus or event. These "induced" ECoG responses have been used experimentally to investigate the neural correlates of a variety of human brain functions, including movement, perception, attention, language, and memory.

In addition to confirming the findings of previous noninvasive EEG studies of non-phase-locked responses, ECoG studies have provided insights into the different spatial–temporal response characteristics of these responses at different frequencies. These studies have emphasized the importance and utility of responses in a broad range of frequencies higher than traditional gamma frequencies (30–60 Hz), thus called "high gamma" (~60–200 Hz). The timing and anatomical distribution of high gamma responses have often been more discrete and specific for putative functional activation than oscillatory responses in lower frequencies, including those in alpha, beta, and even traditional gamma frequencies (see Fig. 1). Although their utility for mapping language cortex has not yet been established, there has been excellent agreement with the results of ESM in somatomotor and auditory association cortices. In contrast, oscillatory responses in alpha and beta frequencies have tended to have a broader anatomical distribution, greater sensitivity to changes in arousal and attention, and a slower responsiveness to functional events. These response characteristics may reflect the action of thalamocortical control circuits that coordinate cortical processing. The response characteristics of broadband high gamma responses, on the other hand, suggest a tighter connection to local cortical circuitry, and their occurrence in nearly every major functional–anatomical domain of the human brain suggests basic mechanisms common to most cortical processing. Consistent with this notion, recent animal studies have found that broadband high gamma responses are highly correlated with

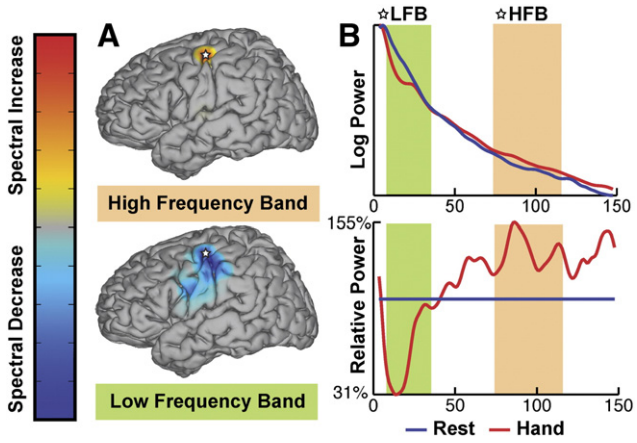

Fig. 1. Example of ECoG signal changes that occur between the tasks of hand opening/closing and resting. (A) ECoG signals in the mu/beta band (5–30 Hz) decrease with the task and are spatially less specific (topography on bottom), whereas ECoG signals in the gamma band (70–116 Hz) increase with the task and are spatially more specific (topography on top). (B) ECoG power, calculated for the electrode marked with a star in the topographies, at different frequencies decreases in the mu/beta band (marked by the green bar) and increases in the gamma band (orange bar). (From Brunner et al. [8], with permission.)

increases in population firing rates [e.g., 7] and may be tightly linked to the occurrence of action potentials. In theory, however, these responses could also be sensitive, particularly at the level of ECoG, to the degree of synchronization in population firing. A related question is whether these broadband responses arise from the spatial summation of band-limited oscillations in overlapping neural assemblies or simply reflect random membrane fluctuations associated with increased synaptic activity. Future attempts to answer these and related questions may be relevant to ongoing debates about the relationship between high gamma responses and neural coding and will likely affect the interpretation of research and clinical studies of ECoG oscillations.

The clinical utility of ECoG spectral analysis, including its sensitivity and specificity with respect to ESM and other mapping techniques, is still under active investigation. To date, this research has already indicated excellent sensitivity/specificity for ECoG mapping in sensorimotor cortex [8,9] and auditory cortex [10], where functional anatomy is densely and predictably organized. In language cortex, however, where function is more widely distributed, the sensitivity of ECoG with respect to ESM has been less than optimal [11,12]. Because ESM induces a temporary and reversible functional lesion, it remains the gold standard for predicting postresection functional impairment. However, with future developments in task design and signal analyses, as well as confirmation against the ultimate gold standard of postsurgical outcomes, ECoG functional mapping is expected to provide an important complement to ESM and other mapping techniques [8].

3. Detecting detailed aspects of behavior in electrocorticographic signals

3.1. Gerwin Schalk

3.1.1. Contrasting ECoG versus scalp versus single cell recording for elucidation of brain behavior

Electrocorticography, also sometimes called intracranial EEG or iEEG, refers to recordings from above the brain but underneath the skull. Thus, ECoG can be recorded using electrodes that are placed below the dura mater directly on the surface of the brain (i.e., subdural recordings) or on top of the dura (i.e., epidural recordings) or using skull screws that penetrate the skull. As such, ECoG signals

are acquired in the continuum between single-unit action potential firings and field potentials that are recorded intracortically (i.e., within the cortex), and EEG signals that are recorded from the surface of the scalp.

Electrocorticographic signals have been recorded in animals (in particular rats, rabbits, cats, and pigs) for several decades [13–23]. Because placement of the electrodes requires an invasive procedure, with very few exceptions [e.g., 24], almost all ECoG-based studies in humans to date have used patients that were implanted with ECoG electrodes preparatory to invasive brain surgery, usually to remove an epileptic focus or mass lesion. In other words, in these human ECoG studies, all implant-related parameters (configuration and location of the electrodes, as well as duration of the implant) have been and are to this date defined by clinical requirements without any regard for research. The electrodes used in these clinical procedures are typically platinum electrodes 4 mm (2.3 mm exposed) in diameter and are configured in either a grid (e.g., 8×8 electrodes) or strip (e.g., 4 or 6 electrodes) configuration with an interelectrode distance of usually 10 mm.

Because the subjects in these human studies have been patients who are being evaluated for invasive brain surgery, many early human ECoG studies were conducted by physicians with an interest in research [25–30]. For the same reason, these studies were often focused on aspects that are relevant to clinical evaluation of this patient population, such as functional mapping of motor or language function. These early efforts culminated in the first comprehensive characterization of ECoG responses to visuomotor tasks in the late 1990s [31,32].

The initial and progressively increasing interest in ECoG was initially based on its improved signal characteristics compared with those of scalp-recorded EEG. Compared with EEG, ECoG has higher spatial resolution (i.e., millimeters vs centimeters [33,34]), broader bandwidth (i.e., 0–500 Hz [35] vs 0–40 Hz), higher amplitude (i.e., 50–100 μV maximum vs 10–20 μV), and far less vulnerability to artifacts such as electromyography (EMG) [36,37]. The implications of the powerful characteristics of ECoG were initially not widely appreciated. In fact, there has been a prevalent conviction in basic and applied neurophysiology [38–41] that only action potentials provide detailed information about specific aspects of brain function. This underappreciation of the capacity of ECoG created opportunities for taking advantage of the good spatial and temporal resolution of ECoG recordings for basic neuroscience investigations and for translational opportunities such as brain–computer interfaces (BCIs).

3.1.2. Definition of BCI and evolving uses of ECoG for BCI innovations

Brain–computer interfaces use brain signals to communicate a user's intent [42]. Because these systems directly translate brain activity into action without depending on peripheral nerves and muscles, they can be used by people with severe motor disabilities. Successful translation of BCI technology from the many recent laboratory demonstrations into widespread and valuable clinical applications is currently impeded by the problems of traditional noninvasive or intracortical signal acquisition technologies. Consequently, the favorable characteristics of ECoG began to attract the attention of the multidisciplinary BCI community. Some of the first research groups that began to evaluate ECoG for BCI purposes were Levine's and Pfurtscheller's groups [43–48]. These studies remained largely isolated efforts until the first online BCI studies [5,6,49–51] ignited substantial interest by the scientific community in ECoG-based studies, initially for BCI research and development, but rapidly also for basic neuroscience investigations and other evolving applications.

Within a few years, ECoG-based neuroscience research demonstrated that ECoG in humans provides substantial information about movements and cognitive functions [5,52–60] (see Fig. 2) and thereby disproved the widespread assumption that such information is available only in recordings from intracortical microelectrodes.

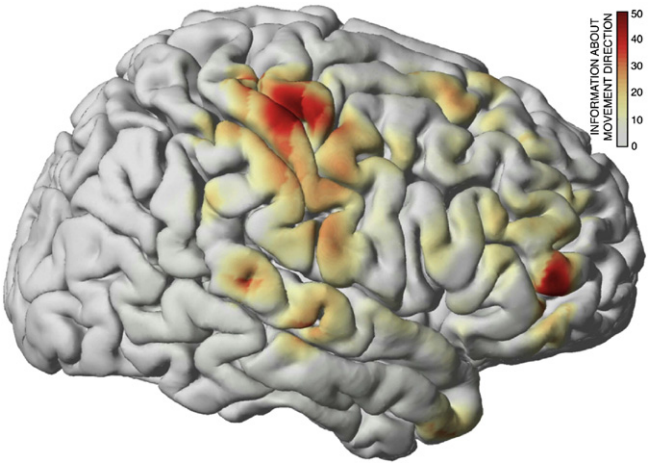

Fig. 2. Electrocorticographic signals give detailed information about hand movement direction. Color-coded shading (see color bar) quantifies, as an average across five subjects, the amount of information about movement direction in different cortical areas. Most of that information is located in hand areas of motor cortex. (From Kipke et al. [63], with permission.)

Other advances are beginning to take advantage of the body of information made available by ECoG. For example, recent studies have shown that task-related ECoG activity can be derived and effectively visualized in real time on a topographical display without the need for extensive post hoc analyses by an expert [8,61,62]. This advance dramatically increases the practical value of ECoG-based imaging for clinical applications (e.g., for functional mapping prior to invasive brain surgery, as described in more detail later in this article).

In summary, traditional ways to interrogate the brain using electrophysiological methods were focused on either scalp-recorded EEG or intracortical microelectrode recordings. With its availability in humans, favorable signal characteristics, and demonstrated information content, ECoG has become an important and increasingly recognized signal modality for different areas of basic and translational neuroscience research.

4. Electrocorticographic brain dynamics using high-resolution recordings

4.1. Robert Oostenveld

4.1.1. Review of current iteration of grid/strip technology and materials

The brain is organized in anatomically and functionally separated regions. Studying the interplay between these regions requires the ability to record the activity from the individual regions. Whereas scalp electroencephalography (EEG), when combined with biophysical motivated source estimation techniques or blind source separation techniques, can approximate the differential activity of different regions, the possibility of recording directly from the brain provides spatially and temporally much better separated signals.

Recording signals on the surface of the cortex (ECoG) requires electrodes to be placed inside the skull and in direct contact with the brain. The most common application of ECoG recordings in humans is localization of an epileptogenic focus and mapping out of cortical functions prior to surgical resection of cortical tissue in patients with medically refractory epilepsy. For this application, an ECoG grid is placed subdurally over brain regions suspected of being involved in the abnormal activity. These grids are usually composed of 16 to 64 platinum disk electrodes 4–5 mm in diameter that are regularly spaced at 1 cm in a rectangular or strip arrangement with a flexible silicon carrier [5,37,64]. As an alternative to surface electrodes, depth electrodes can be inserted into the brain to record activity from deeper regions [65,66]. Multiple ECoG grids can be placed on the

cortical surface simultaneously, combined with electrode strips and depth electrodes [67].

In primate and nonprimate animal models, intracranial or intracortical recordings have traditionally been used to address fundamental research questions. The most common recording technique uses one or a few sharp-tipped needle electrodes that are inserted during the recording session and that record both the firing activity of one or a few neurons and the compound activity as local field potentials (LFPs) of the surrounding tissue [68,69]. Whereas the firing activity represents the action potentials that are the output of a neuron, ECoG electrode grids pick up the LFPs that are thought to mainly reflect the cell membrane fluctuations that are related to the input that the neuron receives. This dendritic input reflects the network that projects onto the neuron, and hence ECoG recordings emphasize the network characteristics [70]. The acute recordings with needles require direct access to the brain during the data acquisition and should be contrasted with the chronic implanted ECoG grids from which data can be recorded with the skull closed after the initial surgical implantation.

The LFPs recorded from animals correspond most closely to the signals that are picked up with ECoG grids in humans. The increasing insight into the role of oscillatory membrane potential fluctuations in dynamically modulating the synchronization between network nodes (reviewed in Fries [70]) boosts the relevance of simultaneously recording LFPs from many areas. This has resulted in efforts to design and manufacture high-density ECoG grids that allow for chronic implantation and the acquisition of data over prolonged periods. The requirements for biocompatibility and long recordings are shared with the potential application of these ECoG grids for human BCI studies and applications.

4.1.2. Advances in grid techniques/materials for high-resolution recordings

We have developed a novel ECoG electrode grid that allows long-term simultaneous recordings over a large cortical area, ranging from primary visual areas in occipital cortex to areas involved in motor planning in the precentral cortex (Fig. 3) [71]. Our grid design is based on micromachining techniques that are developed largely in the context of semiconductor and electrical engineering. The grid consists of a 10-μm thin polyimide substrate on which 252 platinum electrode contacts are deposited using a sputtering technique. The electrode contacts are 1 mm in diameter and cover an area of ~35 × 60 mm with an electrode spacing of 2 to 3 mm. The particular dimensions and spatial arrangement of the electrodes were guided by the requirement of measuring a large part of the left hemisphere of a macaque monkey's cortex.

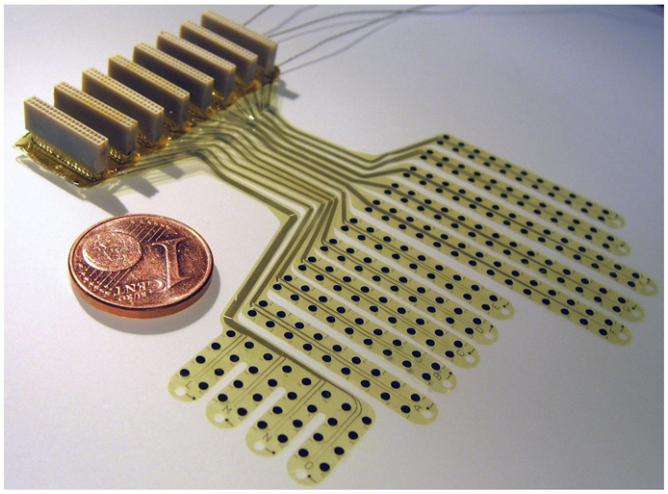

Fig. 3. High-density 252-channel ECoG electrode grid with an optimized geometry for the left hemisphere of the macaque monkey brain. For size comparison, a Eurocent is placed next to the grid. Note the arrangement of the grid in "fingers," allowing it to follow the curved surface of the brain.

The ECoG grid was implanted in two monkeys that were trained to perform a visual spatial attention task. For the task, the monkey fixates a central location and responds by releasing a lever whenever a change is detected in the target, which is one of two stimuli that are simultaneously presented at ~2° of visual angle from the fixation point. LFP signals were recorded while the monkey was awake and performing the experimental task. We recorded ECoG for 4 months in the first monkey and for more than 11 months (still ongoing) in the second monkey. Over time, the quality of the LFP signal remains constant, as indicated by comparisons of single-trial and averaged visual evoked potentials and the stimulus-induced power of physiological frequency bands across recording sessions (see Fig. 12 in Rubehn et al. [71]).

The manufacturing process of the electrode grid has not yet reached the limits for further miniaturization, allowing for smaller interelectrode distances and, simultaneously, a larger number of channels. We are currently investigating the use of polyimide electrode grids to construct multielectrode shaft probes that can be inserted into the cortex, allowing laminar recordings and recordings from deeper areas. A limitation in the recording setup so far was the 256-channel amplifier. The next series of measurements will be performed with a different acquisition setup that will allow at least 1024 and potentially 2048 channels. The combined acquisition of LFPs from the cortical surface with recordings from deeper areas will allow us to study cortical networks with even greater precision. Both the insights into the cortical functioning that are gained from offline LFP analysis and the development of high-density ECoG electrode arrays will increase the possibilities for the use of ECoG in applications for brain–computer interfaces.

5. Using electrocorticographic signals for seizure detection and prediction

5.1. William Stacey

5.1.1. Using BCI technologies in clinical epilepsy

More than 60 million people worldwide have epilepsy (~3 million in the United States), a disease that can produce significant morbidity or death when uncontrolled [72]. The goal of epilepsy treatment is complete freedom from seizures and side effects, but current antiepileptic drugs are ineffective in about one-third of patients. For patients with uncontrolled seizures, particularly those with temporal lobe epilepsy, surgical resection can often be very successful [73]. Unfortunately, even with maximal available therapy, 25% of patients with epilepsy continue to have uncontrolled seizures, resulting in impaired quality of life and increased risk of injury, disability, and death. One new form of treatment is the use of implantable electrical devices to control seizures [74]. There is currently one FDA-approved device for epilepsy (Cyberonics [75]) and two others currently seeking FDA approval (Medtronic [76], Neuropace [77]). It has been established that these devices can be used safely and that electrical stimulation can control seizures. The Neuropace device, known as a "closed-loop" device because it records signals from the surface of the brain and stimulates only when it detects a seizure, has demonstrated that the location and timing of the stimulus can be beneficial. Although all three devices have been effective, they provide only modest improvement. One potential reason for these results is that the devices were all developed several years ago, prior to several technological breakthroughs that are shaping the BCI field. New BCI technology provides the ability to improve epilepsy care through surgical localization, antiepileptic device development, and better characterization of epileptic networks.

Current understanding of epilepsy has been greatly influenced by the spatial and temporal scales of available EEG technology. For more than 50 years, clinical EEGs were limited to sampling rates less than 100 Hz, primarily because of the physical constraints of the pen-and-ink machines used to acquire them. In the past several years, with digital EEG machines that can sample at arbitrarily high rates, several groups have begun to investigate the characteristics of epilepsy in higher frequencies [78–80]. One important finding is that HFOs often correlate with epileptic tissue [3,35,81]. Much of clinical decision making relies on determining the localization of the seizures, often with implantation of subdural ECoG electrodes. The standard spacing of these large electrodes is ~1 cm. Recent recordings with smaller and closer electrodes demonstrate that there is seizure-like activity occurring in smaller tissue volumes than was previously known [82–84]. These technological improvements in spatial and temporal sampling constitute a ripe area of research and are providing crucial new information about the dynamics of seizure generation.

5.1.2. Seizure detection and prediction: a work in progress

A long-standing goal of EEG systems is automatic detection of seizures and epileptiform activity. Most clinical EEG manufacturers include such algorithms, but their practical use remains somewhat limited and to date cannot substitute for human reviewers. The primary difficulty is that seizures are heterogeneous between patients, and developing algorithms to handle that variety is extremely complex. This complexity is a severe limitation in implanted devices, where the computational burden greatly limits battery life [85]. Even human experts have difficulty identifying some seizures [86].

A separate, and more difficult, challenge is to predict seizures before they begin. The search for methods to predict seizures arose from clinical experience: some patients notice when a seizure is approaching, often hours beforehand. Providing this information to other patients would give them a measure of control over this chaotic disease: if patients can be warned of a seizure before it starts, they can treat it preemptively or reach a safe location. Preliminary data also suggest that early intervention is more effective at controlling seizures. Several potential seizure prediction algorithms have been investigated over the past 15 years, but the only clear answer to date is that there is evidence of a “preictal state” [87]. Results have been slow: meetings of the International Workshop on Seizure Prediction have regular “prediction contests” [88], but in the 8 years since inception, there has been very limited success. One important step was defining how to measure predictability [89b], and now several groups are approaching the problem more systematically.

Perhaps the greatest success of the Seizure Prediction Workshops is the establishment of an international EEG database, which is currently under development. The database will provide access to de-identified human intracranial EEGs for training and testing algorithms as well as other basic research. This database will include recordings with smaller electrodes and higher sampling rates, which have not been available for most prior work on seizure prediction or detection. As these data become available, they will provide vast amounts of new data, and researchers are optimistic that better methods of seizure detection and prediction will be developed.

5.1.3. Current progress

There are several ongoing projects dedicated to developing and testing new technologies to improve the spatial and temporal sampling in clinical epilepsy. There are several amplifiers already marketed that record at >10 kHz, although in practice these often need to be independent and in parallel with the clinical systems, which often have hardwired anti-aliasing filters at much lower frequency cutoffs. Likewise, devices are already available with high-density surface [83] or penetrating [82] microelectrodes (Fig. 4). Current research is focused on both evaluating the data acquired with these technologies and improving on them.

Increased resolution is not without its drawbacks: the amount of information can quickly become very time consuming for a human reviewer. Surgical candidates typically are recorded continuously for several days, and with several hundred channels recording at over 1 kHz, each patient generates several terabytes of data. These data need reliable algorithms for automated seizure detection, and methods to detect HFOs are also being developed [35,36,89a]. The electrodes are not easy to connect and at present are normally limited to a few select regions. Several groups are developing improved electrodes for implantation into humans [90,91].

Improved spatial and temporal sampling has broad implications in epilepsy research. Evidence is mounting that these technologies can help localize epileptic tissue in candidates for epilepsy surgery [79,80]. As shown in Fig. 4, higher sampling rates uncover fast activity that is filtered out with traditional EEG settings. This information may prove crucial in developing seizure prediction and detection algorithms, as for the most part it was not available in previous efforts. HFOs are a prime candidate for use as feedback in an antiepileptic device, providing a possible biomarker of epilepsy [74]. And perhaps most importantly, this technology has great potential to help us understand epileptic networks. Seizures and HFOs involve thousands of neurons on a very fast time scale, which can be simulated with computer models [92–94], but is difficult to characterize even in vitro with current technology. As devices become available that can monitor neural activity on smaller and faster scales, we can begin to analyze the complex network dynamics involved.

6. Using electrocorticographic signals for rehabilitation

6.1. Eric Leuthardt

A novel approach to address a diverse spectrum of motor disabilities has been to access the brain directly. This notion is referred to as a BCI, whereby decoding brain signals associated with the user's intentions can be used as control features to allow the individual to more effectively interact with the environment. This brain-derived control is dependent on the emerging understanding of cortical physiology. To date, the majority of brain signals used for clinical rehabilitation have been related to motor intentions. Examples are seen in Pfurtscheller's work in analyzing EEG. His group was one of the first to describe the changes in amplitudes in sensorimotor rhythms associated with motor movement [96–98]. As a result, Pfurtscheller, Wolpaw, Birbaumer, and colleagues have used these signals to achieve basic levels of control in humans with amyotrophic lateral sclerosis (ALS) and spinal cord injury. These types of control allow one to move a cursor on a screen or select letters for simple communication devices. Another example includes the translation of Georgopoulus and Schwartz's findings that neurons in motor cortex, when taken as a population, can predict direction and speed of arm movements in monkeys [99–101]. These findings led to preliminary human clinical trials in which spinal cord-injured patients were able to manipulate computer cursors on a screen [102,103].

Recently, the use of ECoG as a signal for BCI has gained attention as a practical and robust platform for clinical application. ECoG has been posited to be an ideal trade-off for practical implementation [5]. Compared with EEG, the signal in ECoG is more robust, and because the ECoG signal is recorded from larger electrodes that do not penetrate the brain, these constructs are thought to have a greater likelihood for long-term clinical durability [36,104]. The use of ECoG for BCI applications has been studied primarily in motor-intact patients with intractable epilepsy requiring invasive monitoring. Similar to EEG-based BCI systems, the ECoG approach has focused primarily on the use of changes in sensorimotor rhythms from motor cortex. What has been distinct, however, has been the access to activity in high gamma bands with ECoG. Utilization of this activity has provided a significant advantage with respect to training

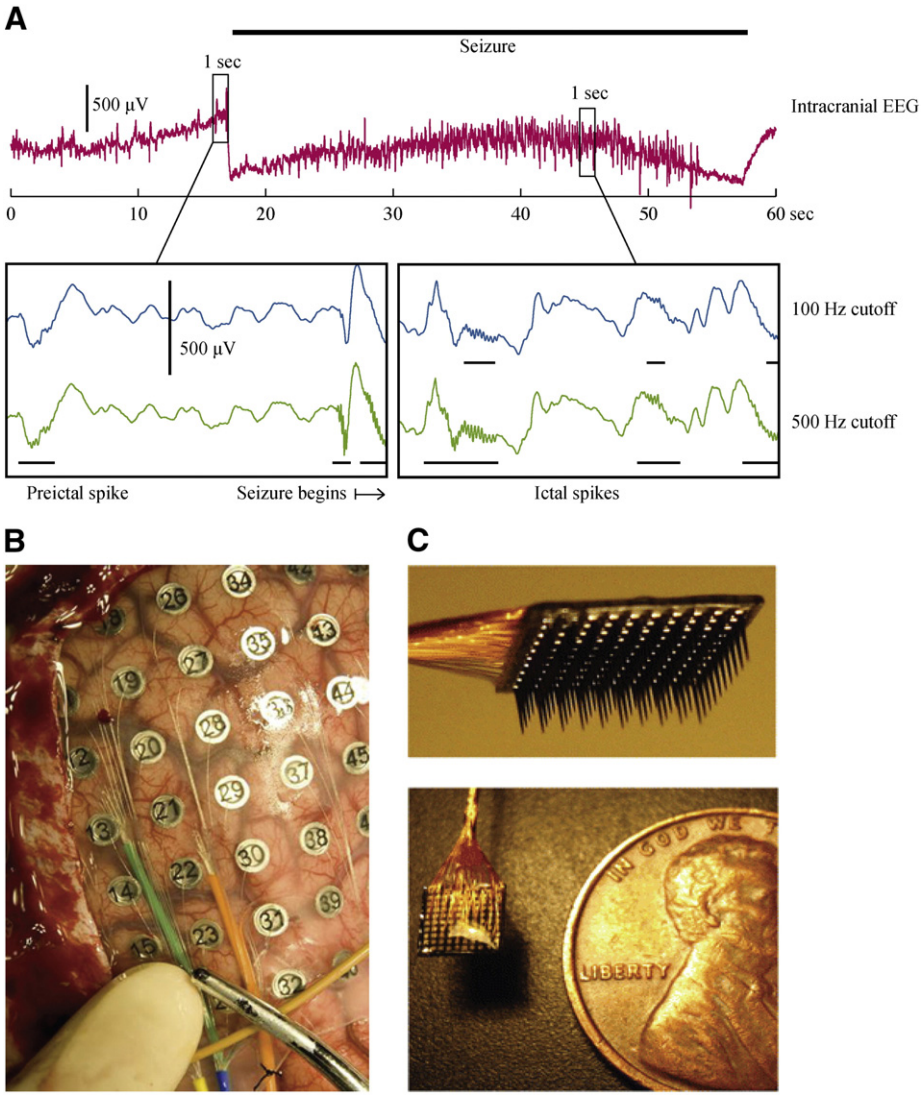

Fig. 4. Using brain–computer interface (BCI) technologies in epilepsy. (A) Improved temporal sampling. Top: A seizure recorded from a standard intracranial electroencephalogram (iEEG) grid electrode in a human patient. This electrode was over the seizure onset zone. Data were recorded at 32 kHz and downsampled to ~2.7 kHz. Insets: Data were filtered with a high cutoff of 100 Hz (blue) or 500 Hz (green) for 1-second epochs just prior to seizure onset (left) and during the seizure (right). Bars indicate the presence of high-frequency oscillations (HFOs), which with 100-Hz cutoff are not present preictally and are much less prominent during the seizure. (B) Improved spatial sampling. Typical cortical grid electrodes are numbered, and several additional microelectrodes are placed on either side of electrode 21 (green and orange wire bundles). These electrodes sample from smaller volumes of brain in the regions not covered by the traditional clinical grids. (From P. House, Department of Neurosurgery, University of Utah, with permission.) (C) The Utah microelectrode array, with 100 penetrating electrodes in a 4-mm-square grid. (From Kelly et al. [95], with permission.)

requirements and multidimensional control [5,6,49,55,58,59]. Because the electrode arrays cover broad regions of cortex, several groups have begun to explore alternate cognitive modalities and their cortical physiologies to expand BCI device control. These have included speech, sensory imagery, auditory processing, and working memory [50,51,105,106].

The ECoG paradigm has not only been used to explore additional control features for BCI applications for patients who have intact cortex but lack motor control (i.e., spinal cord injury or peripheral neuromuscular dysfunction, Fig. 5B); it has also been used to expand the potential patient population for functional restoration where the brain is not intact, namely, in hemispheric stroke. To date, the majority of BCI methodologies are based on a functioning motor cortex that is capable of controlling the contralateral limb. This is the exact situation that does not exist in unilateral stroke (Fig. 5C). In recent years, there has been an evolving appreciation of how ipsilateral motor and motor-related areas participate in same-sided movements in both normal and stroke-affected subjects [107–114]. These findings have prompted further exploration into the underlying cortical physiology as a possible substrate for neuroprosthetic application that could extend BCI approaches for restoration of stroke-induced hemiparesis (Fig. 5D).

Until recently, definitive electrophysiological studies in humans to parse out the manner and extent to which ipsilateral cortex physiologically encodes hand movements have been limited [115–117]. ECoG studies have helped to elucidate this phenomenon and, in turn, extended BCI capabilities. Wisneski et al. [118] used ECoG to more definitively define this physiology in six motor-intact patients undergoing invasive monitoring. Electrocorticographic signals were recorded while the subjects engaged in specific ipsilateral or contralateral hand motor tasks. Ipsilateral hand movements were associated with electrophysiological changes that occurred in lower-frequency spectra (average 37.5 Hz), at distinct anatomic locations (most notably in premotor cortex), and earlier (by 160 ms) than changes associated with contralateral hand movements. Given that these cortical changes occurred earlier and were localized preferentially in premotor cortex compared with those associated with contralateral movements, the authors postulated that ipsilateral

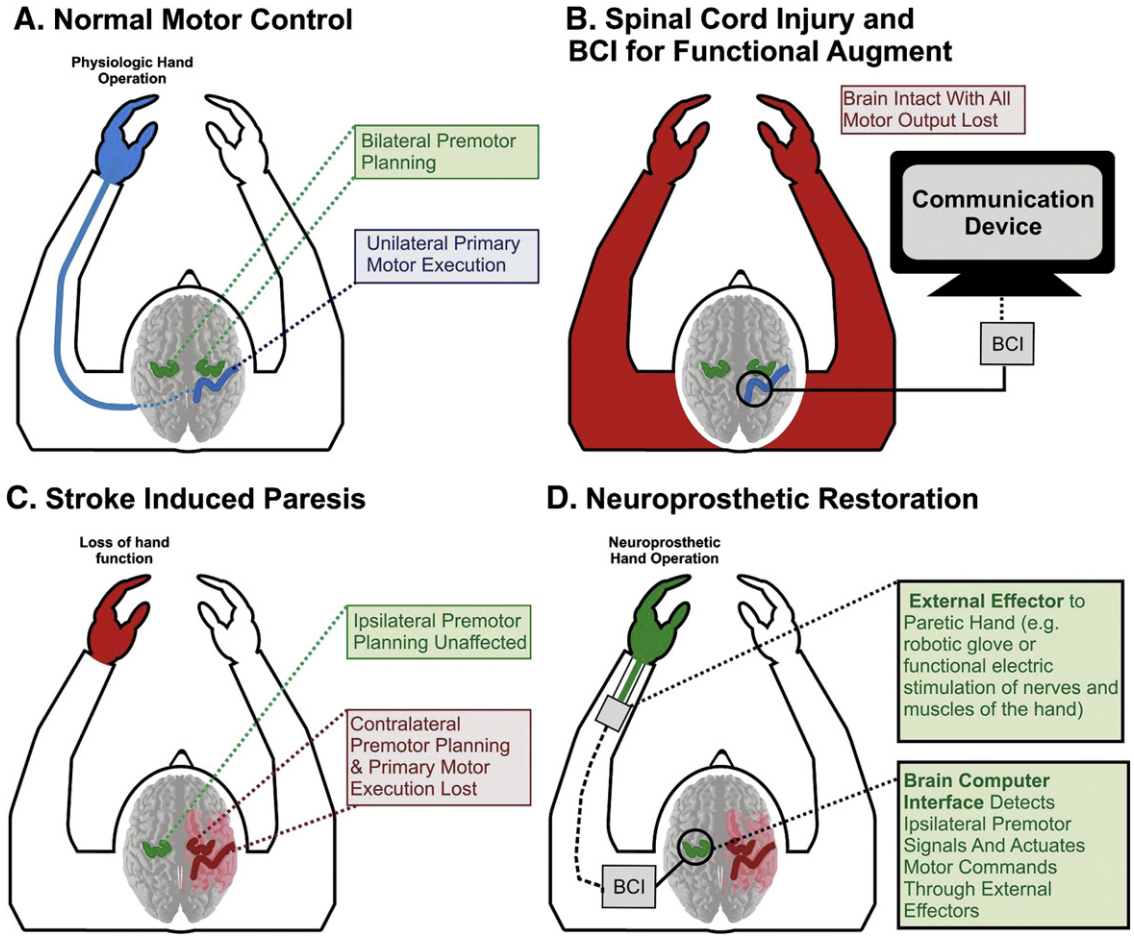

Fig. 5. Concept of how a BCI could be useful for motor disability and stroke. The normal physiological scenario is presented (A) in which motor planning is bihemispherically represented and motor execution is accomplished by the contralateral primary motor cortex. In the setting of spinal cord injury and neuromuscular dysfunction (B), the brain remains intact but peripheral motor control is lost. The motor signals from primary motor cortex are used for communication and control. In the setting of stroke (C), contralateral primary motor and motor associated cortex is lost. Premotor cortex ipsilateral to the affected limb, however, is left unaffected. Thus, in the scenario of hemispheric stroke with contralesional premotor upregulation, a BCI may provide a unique opportunity to aid in actuating the nascent premotor commands. (D) A BCI detecting the brain signals associated with these premotor commands and converting these signals into machine commands that could control a robotic assist device that would allow for improved hand function (i.e., a robotic glove that opens and closes the hand).

cortex is associated more with motor planning than its execution. Additionally, these changes were quite distinct from those changes associated with contralateral motor movements, which were more dominantly associated with higher gamma rhythms (average 106.9 Hz) [118]. In more recent works, the ipsilateral cortical signals associated with joystick movements represent specific motor kinematics (i.e., the direction of the joystick movement) [119,120]. Taken together, in normal motor-intact human subjects, there appears to be cortical activity ipsilateral to the hand and arm movement that is distinct from activity associated with contralateral movements, is associated with planning rather than execution, and encodes specific information about the motor movement.

In the setting of stroke, premotor cortex appears to play a role in patients with poor functional recovery. Functional imaging has shown that these severely affected patients have increased activity in the premotor regions of their unaffected hemispheres [121,122]. Incomplete recovery and its association with heightened ipsilateral activation may reflect the upregulation of motor planning with an inability to execute or actuate the selected motor choice. In this situation, a BCI may provide a unique opportunity to aid in actuating the nascent premotor commands. By detecting the brain signals associated with these motor choices, the BCI may then convert these signals into machine commands that could control a robotic assist device that would allow for improved hand function (i.e., a robotic glove that opens and closes the hand). The BCI would allow the ipsilateral premotor cortex to bypass the physiological bottleneck determined by the small and variable percentage of uncrossed motor fibers. This new methodology would allow for restoration of function in chronically and severely affected subjects for whom methods of rehabilitation have not accomplished a sufficiently functional recovery. The earliest demonstration of ipsilaterally derived control was published by Wisneski et al. [118]. Using electrocorticography, the group demonstrated that control comparable to contralaterally derived control could be achieved by using the anatomic sites or the lower-frequency amplitude changes distinctive to ipsilateral movements.

In summary, the ECoG research paradigm has allowed for a more direct interrogation of human cortical physiology. This has allowed for an expansion of scientific insight into both motor and nonmotor cortical processing and has greatly accelerated the possibilities for BCIs to numerous motor-impaired patient populations.

7. Instrumentation for emerging electrocorticography applications

7.1. Christoph Guger, Peter Brunner

In the 80 years since Berger first recorded EEG activity from the scalp using silver wires and a galvanometer [123], researchers and clinicians have continued to develop better commercial EEG instrumentation and clinical applications that make use of EEG

signals. Commercial EEG instrumentation has been used for decades for three established clinical applications: (1) general diagnosis of epilepsy and other disorders of the central nervous system through visual inspection of EEG signals [124]; (2) localization of epileptogenic cortex through visual inspection of interictal and ictal data in ECoG signals [125]; and (3) mapping of eloquent cortex through electrical cortical stimulation (ECS) for presurgical planning of epileptogenic and lesional cortical tissue resection [126].

These three applications (EEG, ECoG, and ECS) have evolved from mechanical stylus- and paper-based instrumentation to fully computerized clinical bedside monitoring systems (Fig. 6). In this evolution, clinical bedside monitoring systems were designed to deliver a visual impression comparable to that of mechanical systems. Such systems record EEG or ECoG signals from 0.1 to 50 Hz sampled at 256 Hz with 12-bit resolution (i.e., sensitivity of 100 μV). To acquire these signals, EEG recordings typically use 20–64 surface electrodes arranged according to the 10–20 International electrode system [127]. ECoG recordings may use arrays of subdural electrodes in numbers from several to ~200 arranged in 1-cm spacing on multiple grids and strips and implanted above or below the dura. A biosignal amplifier with analog-to-digital converters and a workstation constitute the clinical bedside monitoring system. The workstation stores the recorded signals along with a video stream of the subject's behavior. A clinical investigator then bases his or her diagnosis on the visual inspection of recorded behavioral patterns and neurophysiological signals.

The focus of these devices on only those aspects important to visual inspection has recently begun to show its limitations. For example, recent studies have shown promising emerging clinical applications that could replace or enhance established visual inspection-based procedures. Such applications include seizure detection, localization, and intervention [128], passive mapping of eloquent cortex [31], and BCI communication [129]. Most of these emerging clinical applications, however, require technical characteristics, such as real-time capability and high bandwidth and sensitivity, that established clinical instrumentation typically did not provide.

In response, several manufacturers have begun to design dedicated systems for research purposes. These research systems record EEG, ECoG, or single-neuron data in real time from up to 512 channels, sampled at up to 50 kHz with very high sensitivity (e.g., 24-bit resolution, 250-mV sensitivity). Such a system not only acquires data but can also communicate data in real time to external software. These systems clearly focus on the features needed for emerging clinical applications and not only on those needed for established clinical diagnosis based on visual inspection.

Using these research-grade systems, groups around the world are now demonstrating the efficacy of emerging clinical applications [8,130–132]. To translate these clinical demonstrations into clinical practice, research-grade systems need to evolve into pervasive systems. Such pervasive systems are expected to integrate biosignal amplifiers, analog-to-digital converters, and the digital signal processors into the sensor unit. These systems will need wireless data and power connection to be small enough for chronic implantation.

To summarize, three innovative types of clinical EEG instrumentation have emerged from their beginnings as mechanical systems. These innovations, that is, the clinical bedside monitoring system, the dedicated research system, and the pervasive system, define the past, present, and future of EEG instrumentation.

8. Using electrocorticographic signals for real-time brain mapping

8.1. Anthony Ritaccio, Peter Brunner

Resective brain surgery is often performed in people with intractable epilepsy, congenital structural lesions, vascular anomalies, and neoplasms. Surgical planning of the resection procedure depends substantially on the delineation of abnormal tissue, for example, epileptic foci or tumor tissue, as well as the creation of a functional map of eloquent cortex in the area proximal to that abnormal tissue. Traditionally, different methodologies have been used to produce this functional map: ECS [133,134], functional magnetic resonance imaging (fMRI) [135], positron emission tomography (PET) [136], magnetoencephalography (MEG) [137], or evoked potentials (EPs) [138]. Patients undergoing invasive brain surgery would benefit greatly from a mapping methodology that does not have problems often associated with these current existing techniques, that is, a method that is safe, can be rapidly applied, is comparatively inexpensive, is procedurally simple, and is congruent with existing techniques (particularly ECS).

Task-related changes detected in ECoG recordings appear to have these attractive properties. A number of recent studies have shown that ECoG activity reflects task-related changes [31,32,139–142]. These studies show that ECoG amplitudes, in particular frequency bands, carry substantial information about motor, language, and visual tasks. Specifically, amplitudes typically decrease in the mu (8–12 Hz) and beta (18–25 Hz) bands, whereas amplitudes usually increase in the gamma (>40 Hz) band (see Fig. 1). Furthermore, recent studies demonstrate that such ECoG changes, particularly those in the gamma band, are in general agreement with those derived using fMRI [143], as well as results determined using ECS [11]. Unfortunately, the practical attractiveness of functional mapping by recording macroscopic local field potentials representing neuronal populations involved in a specific task has been severely limited by the need for highly trained personnel and sophisticated offline analysis techniques.

In reponse to this need, we have recently demonstrated a comprehensive evaluation of a robust, practical, and readily available procedure for real-time presurgical functional mapping of eloquent cortex using subdural electrodes [8]. This procedure is based on our BCI2000 [61] and SIGFRIED [144] (SIGnal modeling For Real-time Identification and Event Detection) technologies. BCI2000 is a general-purpose software platform for real-time biosignal acquisition, processing, and feedback (http://www.bci2000.org). SIGFRIED is a signal processing procedure implemented within BCI2000 that can detect and visualize task-related changes in real time without a priori parameterization (e.g., of frequency bands, visualization parameters) by an expert.

We record ECoG signals at the bedside from implanted grids and strips using a typical sampling rate of 1200 Hz. We record baseline data for approximately 6 minutes while a subject is asked to remain relaxed and avoid any movements. To provide a basis for real-time feedback, we use the SIGFRIED procedure to establish a statistical model of the recorded baseline data. In response to visual cues, patients are then asked to perform simple motor tasks (hand or tongue movements), receptive language tasks (passive listening to a narrated passage), or expressive language tasks (verb generation). While a subject executes these tasks, we use SIGFRIED to identify in real time those grid contacts that show activity changes statistically different from the baseline model. Task durations as brief as 15 seconds have yielded localizing results congruous with conventional electrical mapping methods.

We typically use the following signal preprocessing, feature extraction, and feature selection configurations. First, the signal from each grid contact is re-referenced using a common average reference montage. Then, for each grid contact and 500-ms period, the time series ECoG signal is converted into the frequency domain using an autoregressive model with a model order of one-tenth of the sampling rate. Frequencies between 70 and 100 Hz (10 bins at 4-Hz bandwidth) are then submitted to SIGFRIED. During online processing, SIGFRIED uses the established baseline model to calculate for each grid contact the likelihood that the signal at that grid contact is statistically different from the modeled baseline signals. This likelihood calculation is updated about 30 times per second. A

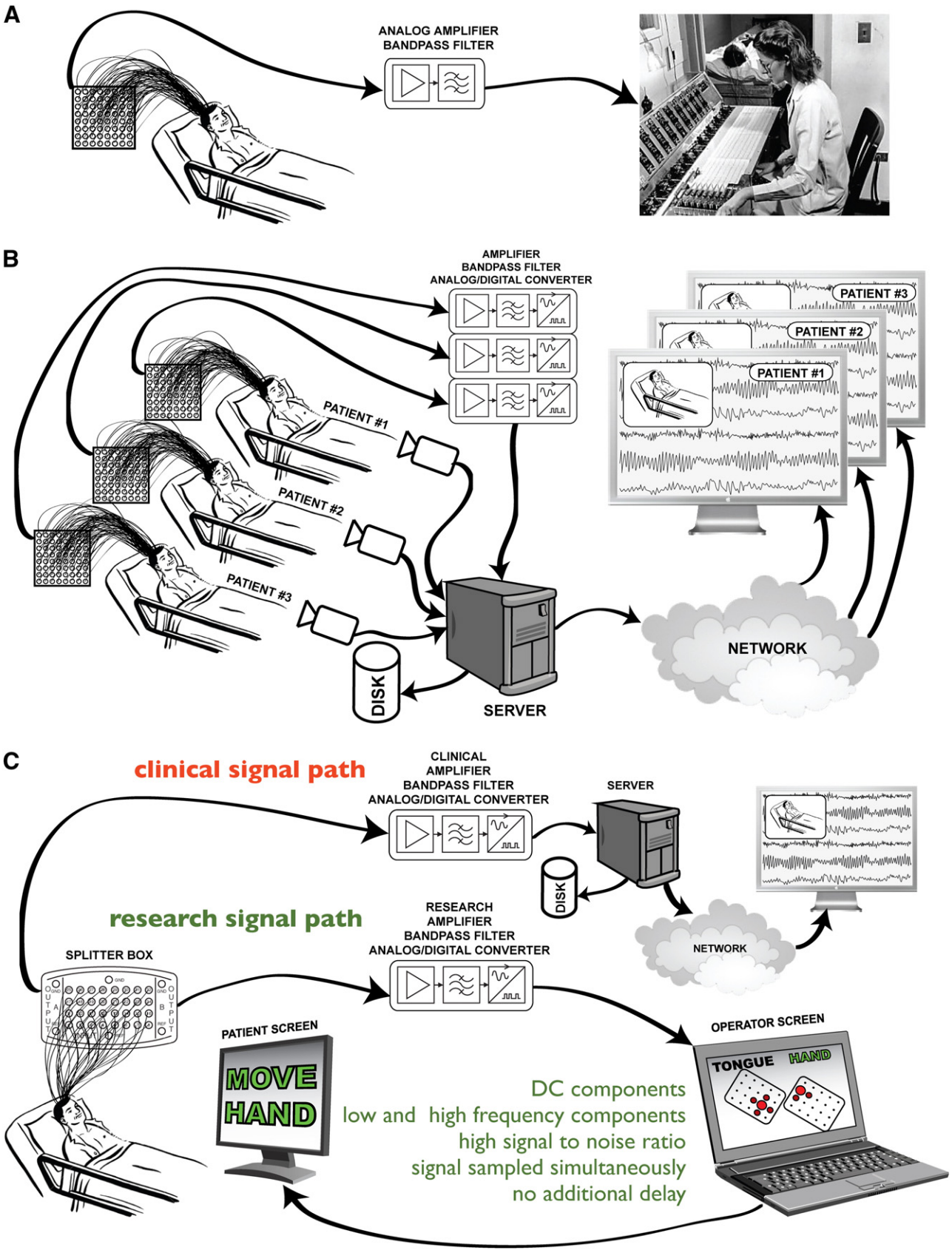

Fig. 6. Concept of clinical EEG instrumentation systems with the patient(s) (left), the instrumentation (center), and the interface to the investigator (right). Mechanical stylus and paper based instrumentation (A) has evolved into digital clinical bedside monitoring systems (B) and, finally, into dedicated clinical research systems (C).

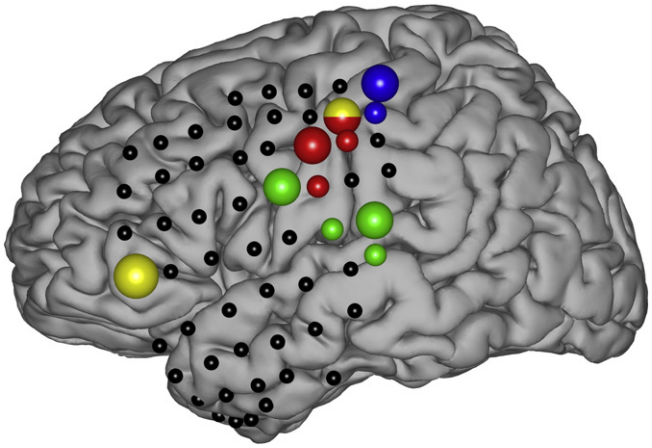

Fig. 7. Results of passive functional mapping using SIGFRIED for one subject in whom 58 electrodes were implanted over frontal, parietal, and temporal cortex. The colored markers indicate those locations whose ECoG activity (as assessed by SIGFRIED) changed during hand/wrist (blue) and tongue/lips/jaw (red) movement, while listening to a narrator (green), and during a verb generation task (yellow). The size of the colored markers indicates the magnitude of change, and black markers indicate electrodes whose activity was not significantly modulated by any task.

computer screen visually displays an electrode topography for each of the tasks. The topographies contain circles at the electrode locations. The radius of each circle expands in real time and in proportion to the ECoG signal change for the respective task compared with the baseline period recorded earlier. Thus, by use of the SIGFRIED/BCI2000 system, clinically relevant mapping of linguistic and sensorimotor function is achievable at the bedside in seconds to minutes (Fig. 7). In our recent multicenter study [8], we found that the SIGFRIED procedure identifies motor sites in at least the same electrodes or their immediate neighbors compared with ECS mapping. Similar comparisons have been made with ECS in the language domain [145]. Furthermore, there is case report evidence documenting similar speed and accuracy in ECoG language assessments during awake craniotomies in the operative environment [146].

The past decade has seen a greatly expanded understanding of task-related ECoG changes. Although the exact relationship between passive ECoG-based mapping and conventional ECS-based mapping is not yet clear, it is likely that passive mapping will play an important adjunctive role in the near future. Thus, we believe that based on its procedural simplicity, rapidity (minutes), safety (passive recording), and relatively low expense, our methodology has the potential to complement and potentially replace currently used clinical methods. These results may have important implications for functional localization prior to invasive brain surgery. This method can be used with little training, can be implemented in the chronic monitoring unit environment, and has also shown early promise in the operative theater as well. The system is currently in evaluation by a number of surgical epilepsy centers in the United States and Europe.

9. Conclusion

9.1. Anthony Ritaccio, Gerwin Schalk

The contributions described above reflect the content of the First International Workshop on Advances in Electrocorticography and thus provide a snapshot of the existing and emerging understanding of the theory and application of electrocorticographic recordings. The success of this first workshop and continuing and growing enthusiasm for this recording modality encourage further workshops on this topic.

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