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A Brief Review of Brain Signal Monitoring Technologies for BCI Applications: Challenges and Prospects

Bashir I. Morshed[1*] **and Abdulhalim Khan**[2]

[1]*Electrical and Computer Engineering, The University of Memphis, Memphis, USA*

[2]*School of Public Health, The University of Memphis, Memphis, USA*

***Corresponding author: Bashir I. Morshed,** Electrical and Computer Engineering, The University of Memphis, Memphis, USA, Tel: 901 678 3650; E-mail: bmorshed@memphis.edu

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Abstract

Significant strides have been made since 1940s for monitoring brain activities and utilizing the information for diagnosis, therapy, and control of robotic instruments including prosthetics. Monitoring brain activities with brain computer interfacing (BCI) technologies are of recent interest to due to the immense potential for various medical applications, particularly for many neurological disorder patients, and the emergence of technologies suitable for long duration BCI applications. Recent initiatives are geared towards transforming these clinic centric technologies to patient centric technologies by monitoring brain activities in practical settings. This paper briefly reviews current status of these technologies and relevant challenges. The technologies can be broadly classified into non-invasive (EEG, MEG, MRI) and invasive (Microelectrode, ECoG, MEA). Challenges to resolve include neuronal damage, neurotrophicity, usability and comfort.

Keywords Brain computer interfacing; Invasive BCI; Non-invasive BCI; Neuronal damage; Neurotrophicity; BCI applications

Introduction

The human brain consists of 86 billion of neurons that communicate information through electro-chemical action potential, an endogenic bioelectric phenomenon, and preserves these information in 1014-1015 synapses as increased connectivity through these induced processes [1]. Brain connectivity can be categorized into three types: Neuroanatomical connectivity that is based on structures of synapses, Functional connectivity that has statistically significant dependence, and Effective connectivity that is dynamic directional interactions among brain regions [2]. Action potential of a single unit (neuron) has an electrical discharge characteristic that can be recorded by intracellular electrodes. Activities of a collection of neurons at a proximal location can be recorded through extracellular electrodes as local field potential (LFP) or as neural firing. LFP is recorded by filtering the electrode signals through a low pass filter (1-100 Hz), while the neuron firings are detected through a spike discriminator [3]. Such endogenic electrical activities are recorded through microelectrodes placed inside the brain cortex or at the surface of the brain cortex (invasive). The electrode converts the ionic current of neurons to electronic current, which can be recorded through a high-impedance electrical sensing circuit [4-6].

Brain computer interface (BCI) which performs four distinct tasks: translating neurological input signals into electrical signals, extracting features from the signals, deriving meaningful information, and aggregating knowledge for useful purposes [7]. Even though early work on brain activity recording was performed in '40s before pacemaker or defibrillators were developed, recent advancements in low-power, wearable embedded systems technology and cyber-physical systems (CPS) have demonstrated the promise of real-time brain activity monitoring for patient centric diagnostics, therapy, and even preventative, proactive monitoring for well-beings [8-11]. For the modern information intensive and demanding workloads, it is frequently required to have quantitative metrics for individual and collective engagement assessment in multiple tasks simultaneously [12]. Understanding this critical connectivity, activations, and mechanism are necessary for developing strategies and rehabilitation therapies to aid in various treatments. However, understanding brain functions is based on two critical factors - the correct identification of the active brain regions, and determination of the functional interactions among the neural assemblies across various brain regions [2]. Research on this grand scale challenge has been highlighted by large-scale initiatives such as the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative [13]. This review outlines various brain monitoring technologies for BCI applications and current challenges for long-duration practical applications.

Technologies for Brain Activity Monitoring

Figure 1 shows a general classification of various technologies currently available for brain activity monitoring. These technologies often referred to as BCI, can be performed at the vicinity of neurons inside the brain cortex, on the scalp, even remotely [14]. The invasive techniques require complex and clinically perilous brain surgery, and as such are only utilized when there are critical or significant clinical needs. On the other hand, the non-invasive procedures can be performed generally without medical complicacy. Table 1 shows a comparative look at the various technologies with few typical parameters along with key advantages and disadvantages. The typical electrode locations for various BCI technologies are schematically shown in Figure 2, and typical signals of some common technologies are depicted in Figure 3.

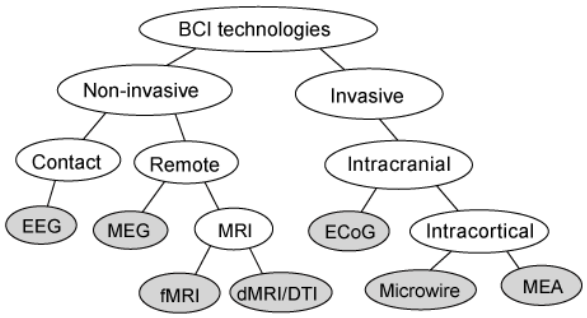

Figure 1: General classification of currently available brain activity monitoring BCI technologies. Technologies: EEG (Electroencephalography); MEG (Magnetoencephalography); MRI (Magnetic Resonance Imaging); fMRI (Functional MRI); dMRI (Diffusion MRI); DTI (Diffusion Tensor Imaging); ECoG (Electrocorticography); MEA (Multiple Electrode Array).

Technologies	Underlying physical activity	Electrode placement	Measurement frequency range	Typical amplitude	Spatial resolution	Temporal resolution	Key advantage	Key disadvantage
EEG	Synchronous neuronal activities (potential)	Scalp contact (usually cap)	0.1 Hz to 100 Hz	Less than 100 μV	1 cm	1- 5 ms	Non-invasive, portability	Spatial resolution
MEG	Synchronous neuronal activities (current)	Remote (eg. helmet)	2 Hz to 100 Hz	Less than 10−14 Tesla	2 – 3 mm	~1 ms	Non-invasive	Non-portability
MRI	Increased blood flow at cortical lobes	Remote (bed inside a tubular equipment)	-	-	1 – 10 mm	1 – 2 s	Non-invasive, non-contact	Non-portability, temporal resolution
ECoG (or iEEG)	Local field potential	Intracranial, cortical surface	1 Hz to 100 Hz	Several hundred μV	0.5 – 3 mm	~1 ms	Signal quality, spatial and temporal resolution	Surgery requirement, highly invasive
Microelectrode (or Microwire)	Extracellular action potential	Intracranial, intracortical	0.5 – 5 kHz	A few mV	~100 μm2	0.1 ms	Signal quality, spatial and temporal resolution	High risk surgery requirement, gliosis and other medical complication
MEA	Extracellular neuronal activities from multiple sites	Intracranial, intracortical	0.5 – 5 kHz	A few mV	~100 μm2 at each site	0.1 ms	Signal quality, simultaneous monitoring of multiple sites	High risk surgery requirement, gliosis and other medical complications

Table 1: A comparative table of various brain activity monitoring technologies [1,3,9,15-17].

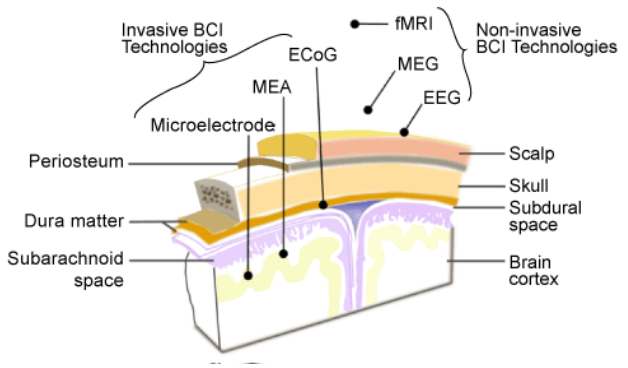

Figure 2: Typical electrode placement locations for various brain sensing technologies.

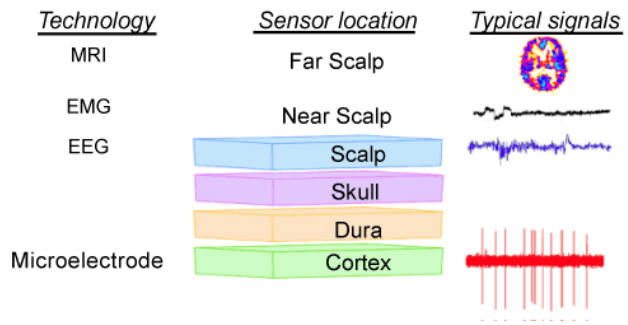

Figure 3: Typical signals for various BCI technologies and sensor location.

Invasive BCI Monitoring Technologies

Implantable, intracranial cortical neuronal devices are highly invasive. Often such implantable medical devices attach to the outside or inside of the skull containing electronic signal processing elements connected to one or more electrodes that penetrates the skull to record neural activities in brain, or to stimulate neurons of the brain in a safe and predictable manner [15-17]. Recording of neuronal activities of the brain can be in form of LFP as used in ECoG, or neuronal action potentials as used in neuronal microelectrode or microwire [15]. Multiple Electrode Array (MEA), sometimes referred as multiple microelectrode or microwire, is commonly used to simultaneously probe a dense region of cortical surface from multiple sites. These approaches have their roots in the pioneering studies conducted by Fetz and colleagues in the 1960s and 1970s [18]. ECoG recording represents the synchronous activity of multiple neurons or multi-units (known as multi-unit activity, MUA), whereas neuronal action potential recording is from ensembles of single neurons (known as single-unit activity, SUA) recordable by microwire or microelectrode. The later can also be used to stimulate individual neuron such as deep brain stimulation (DBS). ECoG electrodes penetrate the skull, but do not penetrate pia mater, while the microelectrodes and MEA penetrate pia mater. DBS is a mechanical neuronal electrode setup that penetrates deep inside the cortex, where these electrodes, even though usually used for stimulation, can also be used for monitoring of neuronal activities. SUA microelectrodes for neuronal action potential recording are intra-cortical, requiring penetration of dura matter and brain cortical tissue, and regarded as highly invasive device [19,20].

Microelectrode or Microwire

One of the invasive electrodes for monitoring of cortical neuron activities is microelectrode or microware. Microelectrode technique has been developed to perform dual purposes: sensing and stimulation. These electrodes are more neuron specific as they penetrate the pia matter and the cortex to have a higher spatial resolution. They can potentially record the activity of a single neuron by recording the potential spikes or action potential of the neuron. These spikes are recorded extra-cellularly by placing electrode within the field generated by the neuron, usually within about 150 μm from the source neuron [21]. Recording from one neuron is called single unit activity (SUA) and recording from multiple brain neurons are referred to as multi-unit activity (MUA) [18]. Microwire electrodes and microelectrode array (MEA) require the penetration into the cortex made possible by microscale and nanoscale technology [22].

As about 30,000 neurons/mm3 is found in the human cortex, hence it is likely that an 80 μm stainless steel microwire used by Strumwasser would be in close proximity with many neurons [15]. The signal can be readily used to record neuronal population activity, or decoded using difference in spike amplitude to determine a single neuronal activity. Electrode design is a key component of microelectrode sensing technique. Among various designs, insulated tungsten wire with exposed tip and stainless steel are two popular choices [15]. Low-power implanted or wearable embedded systems can be used to collect, process, analyze, and wirelessly transmit neuronal data to monitor brain activities remotely [20].

Multiple Electrode Array (MEA)

Invasive electrodes with multi-electrodes include microwires in planar silicon probes and platforms with micro-electrode array (MEA) [21], as well as the so-called "Michigan Electrode" and "Utah Electrode" [22]. The fabrication involves the use of integrated circuit technology to create dense arrays of thin film electrodes. The history of multi-electrode cortical probe dates back to 1966 developed at Stanford University [23]. The structure had a substrate with an area of exposed metal for sensing or stimulating while the rest of the lead is insulated with inorganic dielectrics. However, it was difficult to produce such electrodes until the microelectromechanical systems (MEMS) technology was developed along with Boron etch stops, reactive ion etching and silicon-on-insulator (SOI) wafer technologies. To date, a wide variety of cortical devices were explored with different substrates including silicon, glass, sapphire, and polymers. Among these, silicon is more commonly used because of ease in microstructure fabrication and biocompatibility as required for invasive electrode [23]. "Utah Electrode" produced by the University of Utah is a silicon based MEA with a 100 electrodes that is fabricated such that the tips are coated with platinum, whereas polyimide is used to insulate the whole shank [15]. It is reported to be the best suited to record in the horizontal domain [24] through its conducting parts that are coated with gold along the back of the needle like shanks. "Utah electrodes" are still among the longest functional chronic implants [23].

"Michigan Electrode" array is also silicon based, and has several conducting sites on each shank with a higher concentration of recording sites per microelectrode. Fabrications of these electrodes

require deep Boron diffusion of the shanks and deposition of upper dielectric layer. Titanium-Iridium is defined by a lift off process, then the wafer is dissolved and individual electrodes are released by etching with ethylene diamine pyrocatechol (EDP). The active type of "Michigan Electrode" contains integrated CMOS circuitry on them, whereas the passive type does not contain circuitry [21].

Electrocorticograph (ECoG)

ECoG, sometimes referred to as Intracranial Electroencephalogram (iEEG) [21], is performed with the signal recording electrodes placed at subdural layer [18]. ECoG is primarily developed for sensing to record neuronal activity without penetrating cortical tissue. ECoG records continuous signals from a population of neurons, such as LFP and synchronous spike activity, in contrast to the action potential signals like SUA. This technology has been used for recording of neuronal activity in patients with pre-surgical epilepsy as a part of diagnostics, which has made it possible to study ECoG in human subjects [25]. It can be considered as the least invasive form as electrodes do not penetrate the pia mater and the cortex, even though it penetrates the skull. Compared to EEG or MEG, the electrode of ECoG has the advantage of being placed at a closer proximity to the cortex inside the skull, thereby reduced dampening and deflective effects of the neural signals to be recorded. However, implanting ECoG electrodes require surgical procedure to access inside of the skull for implantation of electrodes that could lead to medical complicacy such as traumatic operation, risk of damage to the brain, and the possibility of infection. ECoG exhibits a higher spatio-temporal resolution, superior signal-to-noise ratio (in particular at high frequencies), and is less prone to artifacts [25,26]. ECoG is able to record higher gamma frequency (>30Hz), consequently provides higher accuracy and shorter training times compared to EEG for external robotic control [27].

ECoG electrodes are usually Platinum/Iridium (Pt/Ir) strips that are designed for short-term use in humans. Exceptions include an ECoG electrode used as the sensing element for a seizure-control device (in FDA approval trial in 2008 by NeuroPace, Inc., Mountain View, CA) [28]. While ECoG appears to be a highly effective modality for BCI control, current studies are constrained by the parameters of epilepsy surgery. Furthermore, electrode placement is solely determined by the requirements of epilepsy surgery. In addition, between recovery of the patient from electrode implantation and electrode removal there is often very limited time, and sometimes limited patient interest, to perform BCI experiments [29].

ECoG signals were used to decode a limited set of discrete hand movements [9,30], as well as continuous movements, such as hand-controlled cursor movements for periodic circular motion, target reaching, flexion of fingers, and upper limb movements [30]. The applicability of online ECoG-based BMIs has been demonstrated. However, long-term stability of ECoG-based devices needs to be further investigated. Zenas et al. customized multichannel ECoG electrode arrays (Unique Medical, Japan) containing 2.1 mm diameter platinum electrodes (1 mm diameter exposed from a silicone sheet) with an inter-electrode distances of 3.5 mm were chronically implanted in the subdural space in two Japanese macaques. Thirty-two electrodes were implanted in the right hemisphere, covering from the prefrontal cortex (PFC) to the primary somatosensory cortex in a primate (monkey A), and 64 electrodes were implanted in the left hemisphere, covering from the PFC to the parietal cortex in another primate (monkey K). They demonstrated the long-term asynchronous decoding of high degree of freedom, arm kinematics in monkeys using these ECoG signals.

Takufumi et al. used ECoG in stroke patients to decode 3 simple hand movements and revealed that the state and movement type of the patient's hand were predicted with an accuracy of 79.6% (chance 50%) and 68.3% (chance 33.3%), respectively [31]. Using the trained decoders, the onset of the hand movement was detected within 0.37 ± 0.29 seconds of the actual movement. At the detected onset timing, the type of movement was inferred with an accuracy of 69.2%.

Other electrode types

Another types of electrode penetrating cortex of human brains are the cone electrode from Neural Signals, Inc, (Deluth, GA) and the platform array made by I2S Implantable Microsystems (Salt Lake City, UT) that are currently being evaluated for clinical use [21]. The cone electrode has 1, 2, 3 and 4 gold-wired electrodes within a glass cone [32]. The electrode assembly involved the use of glass cone that penetrates the cortex, and is embedded with neurotrophic factors. The neurotrophic factor stimulates the growth of neurites that eventually forms a bridge between the cortical neurons and the electrode-teflon coated gold wires. The glass cone tip is about 50-100 μm in diameter though which neurites grow to interface with the gold wires. The gold wires were coiled using a hand-wound mandrill to provide for strain relief in X, Y, and Z dimensions. It is tapered at the edge to allow a maximum length of penetration into the cortical layer. This has been used for chronic cortical implantation and was found to be functional for up to four years in one of the subjects till the subject died from the underlying disease [32].

Other wire electrodes used in non-humans include formvar coated platinum-iridium (90%-10%) microwire (California Fine Wire, cat. #100-167) [31]. Recently, conducting biopolymers are being studied for the use as electrode and not just as a coating material. They have the advantage of less rigidity compared to metal wires and better Young's Modulus when considering that of brain tissue [29]. Another type of invasive electrode is ceramic-based arrays that used 99.6% alumina as the conductor [24]. This invasive electrode was reported to be able to record neuronal activities for at least 3 weeks when implanted in rats.

Non-invasive BCI monitoring technologies

Predominant technologies that can non-invasively monitor brain signals are EEG, fMEG, and MRI. Among these non-invasive sensing techniques, EEG and MEG have excellent temporal resolution, while MEG and MRI have higher spatial resolution. MEG captures magnetic signals generated from neuronal firings, while EEG captures noisy electric signals directly [2,33]. In contrast, fMRI is an indirect measurement of activities since it captures increased blood flow in the cortex that relates to increased brain activities. MEG primarily records activity of only sulcus (normal components of cortical tissue), in comparison to gyrus (tangential components of cortical tissue), while EEG captures both activities. As both MEG and MRI require high sensitive magnetic sensors (e.g. superconducting quantum interference device, SQUID) and a magnetically shielded room (MSR), as well as restriction of subject movement to reduce motion artifacts, these technologies are not suitable for monitoring patients outside of clinical or laboratory settings [34,35]. In contrast, EEG sensors are miniature and lightweight, and can be conveniently worn for continuous sensing at home or outdoors for long duration. Among these non-invasive sensing techniques, EEG and MEG have excellent temporal resolution

(up to 1 ms), while MRI have higher spatial resolution (up to 1 mm) [1,2].

In contrast, Electromyogram (EMG) signals are produced by skeletal muscles and can be primarily associated with facial expressions, as well as physiological and mental states (e.g., sleep and medical abnormalities) [4,6]. EMG signals (typically in the hundreds of μV to tens of mV range) are of typically 7-20 Hz, and allow monitoring of sleep apnea, activation level, and some other medical abnormalities. The sensor position allows proximal detection of certain muscle activities (e.g., eye muscle movement can be detected with sensors placed on the forehead). Between the two kinds of EMG sensors (surface and intramuscular), the surface EMG sensors are less invasive and rugged having the tradeoff of weaker signal strengths and low spatial resolution.

Electroencephalography (EEG)

Non-invasive human scalp EEG is the recording of asynchronous activation of the massive amounts of neuron firings in the brain cortex that produce many oscillatory waves. These waveforms originating from various regions of the brain lobes have been related to specific brain activities representative to certain mental states, stimulation, engagement, cognition load, mind wondering, and other activities. EEG signals are typically in the ten to hundred μV ranges, and classified as delta rhythm (0.1-3.5 Hz), theta rhythm (4-7.5 Hz), alpha rhythm (8-13 Hz), beta rhythm (14-30 Hz), and gamma rhythm (>30 Hz) [36]. EEG analysis has been applied for neuroscience, cognitive science and psychology through studies that show various brain lobes are responsible for specific cognitive activities [37-40]. For instance, the frontal lobe is highly associated with problem solving, mental flexibility, judgment, creativity, foresightedness and deficiencies; whereas the temporal lobe is primarily responsible for auditory sensation, perception, language comprehension, long-term memory and sexual behavior. EEG data can be analyzed to assess mental states and neuronal activities of neurological disorder patients [41]. For epilepsy neurological disorder patients, ictal episodes captured in EEG data shows increased level of uncontrolled activity of brain signals typically characterized by increases in Gamma rhythms [42]. EEG sensors can monitor brain electrical activities for long duration while unobtrusive to the users [43]. EEG sensors are miniature and lightweight for convenient ambulatory wearing and continuous sensing [14]. Such a system can be built with the new cutting-edge embedded technology consisting of an onboard microcontroller with dedicated input and output ports with specific functionalities that can operate independently while collecting data within natural settings [44-46].

Megnatoencephalography (MEG)

MEG technique records magnetic response of the axon current flow using very highly sensitive magnetic coils placed on the scalp. Based on Maxwell Theory, the current flow in neurons produces tiny magnetic fields around them. MEG, in particular, primarily records activity of sulcus, in comparison to gyrus, as the current flow is perpendicular to the sensing coils [2,33]. MEG sensors generally employ special type of magnetic sensors, such as SQUID [34,35]. These passive sensors can record weak magnetic field around 10-14 Tesla. MEG technology allows a user to imagine movement of a limb, increasing or decreasing sensorimotor rhythm amplitudes, known as evoked response [8]. MEG is well-suited for recording of evoked responses in the primary sensory and motor domains, where time- and phase-locked stimulus driven activations predominate. Despite the advantage of high spatial and temporal resolution, MEG has not yet been widely adopted as a cognitive neuroimaging technique [47]. This is primarily due to the large, expensive, and inconvenient helmet with SQUID sensors that renders itself non-portable and highly sensitive to movement.

Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging (MRI) is a relatively new technology that was developed 20 years ago to non-invasively measure patterns of brain activities [48]. MRI technique relies on the resonance of bodily fluid, primarily blood, to orient and resonate to the direction of applied high magnetic field (7–11 Tesla). The magnetic field strength of such equipment is 5 orders of magnitude higher than the Earth's surface magnetic field (25 to 65 micro Tesla). This technique is suitable for human brain activity monitoring where invasive methods are not required. Two types of MRI technologies are common for brain signal monitoring: functional MRI (fMRI), and diffusion MRI (dMRI) or Diffusion Tensor Imaging (DTI). For fMRI studies, low temporal resolution of the blood-oxygen-level dependent (BOLD) signal is a limiting factor [34,35]. fMRI is an indirect measurement of brain activities as it records increased blood flow in the cortex that represents increased brain activities. Scanners that produce very high magnetic fields need to be used for fMRI to improve on the spatial resolution. The measurements can be repeated temporally to obtain sequence of brain images that can be related to brain dynamics. The setup requires the patient to be positioned inside the equipment, thus this technique can rarely be use used for brain activity measurement in real-life settings. DTI technique is usually used to examine structural connectivity of various brain lobes, and convey information regarding the fiber tracts [2].

Other emerging technologies

Positron Emission Tomography (PET) of brain imaging requires introduction of radionuclide tracer on a biologically active molecule inside the body, and 3-dimensional imaging is reconstructed from a pair of emitted gamma rays indirectly by positron-emitting [49]. Among newer technologies for remote sensing of brain activities, near infra-red (NIR) sensing is promising [50]. The technology utilizes the same BOLD phenomenon as fMRI, but attempts to sense increased blood flow through the scalp and skull with NIR transmitter-receiver pairs. Another promising technique is the use of passive LC resonance circuit for capacitive sensing which has been shown to sense biosignals reliably, such as cardiac rhythms, and to some extent for brain signals [51,52].

Challenges of BCI Technologies

The invasive nature of ECoG and MEA electrodes raised a lot of biological and medical challenges. The subject needs to be properly evaluated pre-surgically and the location of the implant identified precisely. The spatial accuracy to localize the cortical position depends on the technology applied and may be done using many of the non-invasive technologies available. Neuroplasticity changes the brain schema in amputated and other neurologic patients for motor, sensory and other cortical areas and appears to be a continuous process. Phantom phenomena could be evoked in amputated patients and fMRI used to localize the cortical areas in which the neuronal activity is of interest for implantation of the cortical device [53]. Intra-operative cortical mapping is also done in neuro-oncology during brain tumor excision to salvage vital brain areas such as speech.

Reducing size of invasive electrode is now possible but is becoming a trade off with mechanical strength considering the process of implantation. The tips of the invasive electrode need to withstand the resistance of the pia matter and brain tissue during implantation [23]. However, inflammation is less on smaller materials and polymer fibers of 2–12 μm was found to have no macrophage adherence in cell culture [22]. Such intracortical penetration of electrodes inside the brain requires rupturing of blood brain barrier (BBB), which might lead to unwanted consequences such as epileptic seizures [54,55]. Biocompatibility is achieved by choosing biocompatible materials and further encapsulating with biopolymers [23]. Tissue reactions are identified on histological examination of brain tissues after periods of implantation in animals [56].

Neuronal damage

Neuronal damage is discussed within the context of invasive electrode as an implant. Preexisting pathological conditions, which may have progressive neural degenerative characteristics such as amyotrophic lateral sclerosis (ALS) would not be considered in this discussion of neuronal damage [57]. The implant procedure is traumatic and neural damage starts during surgery. Several insertion techniques have been developed over time that varies from manual insertion onto the brain of an invasive electrode to the use of insertion tools. The use of insertion tools can give a guide to the surgeon on the speed of insertion. Some evidences suggest that mechanical insertion gives better results for recording and stimulation [58]. It is also observed that faster speed of insertion of invasive electrode into the cortex yield better outcomes, fast speed of insertion of 2000 μm/s was the only condition that tissue damage was not observed in ex-vivo studies [59]. Up to 40% of neuronal loss within 100 μm of invasive electrode was observed by Tresco et al. [60], with neuronal loss observed as early as 2 weeks. This affects the quality of signal recording. The goal of every invasive electrode is to achieve stable signal recording or stimulation [22].

Furthermore, neuronal stress and damage occurred when invasive electrode inserted at 0.5 mm/s – 1mm/s compared to 50 μm/s as evidenced by greater alteration in pH and longer duration of acidosis at slow speed insertion [58]. Studies also show conflicting results for multi shank and single shank invasive electrode insertion sped and its effect. However, Bjornsson et al. reports that no significant difference was observed between different devices with different tip types [59]. Regardless of speed of insertion, many other factors associated with neuronal damage at insertion of invasive electrodes such as depth of insertion and accompanying vascular damage. The cerebral cortex is about 2mm thick and divided into 6 layers, and the depth of insertion is determined by the cerebral layer of interest [61]. Complete cortical neurovascular mapping is done with two-photon mapping and this mapping can be used to avoid surface vessels. Surface vessels are found to deviate 49 μm to 500 μm from an electrode during insertion, hence recommended that penetrating invasive electrodes should be limited to a depth of less than 49μm from a surface vessel during insertion. Trauma to vasculature would lead to bleeding and acute tissue damage. In addition, this could severe the blood supply to surrounding tissue leading to cell death. Bleeding into interstitial space of the brain may lead to pressure effects and extracellular accumulation of fluid (edema), which further increases ischemia and neuronal compromise. Post-surgical prophylaxis to avoid raised intracranial pressure is usually observed. This can only reduce edema but the trapped erythrocytes in the interstitial space are potentially toxic if it undergoes lysis with the release of heme and globulin. The erythrocyte is phagocytosed by microglia and hematogenous macrophages, with some residual inflammatory effect. This leads to further neuronal loss [62].

The constant presence of invasive electrode in the host tissue also results in biological response [22]. Tissue reaction to invasive electrode and stab wounds on other subjects using same type of invasive electrode were compared and found the former had more intense and prolonged inflammatory response [60]. The mere presence of an invasive electrode would mean that some tissue have been displaced to accommodate it, this has been found to alter pH in brain tissue and found to correlate with size [58].

Acute reactions include brain edema, which can lead to increased level of intracranial pressure if not managed [23]. Edema in the immediate surroundings of the electrode increases the distance of electrode from the neurons and is responsible for the reduction in signal quality and increased impedance within the first 3 days following implant [63]. Early tissue response starts within hours following device insertion. It is characterized by an astrocyte and microglial response in the surroundings of the device [15]. The response is proportional to the volume of the invasive electrode within the brain tissue. Microglia release nitric oxide, cytokines and other toxic molecules which cause neuronal death, and activation of astrocytes. Astrocytes make up about 40-65% of glial cells in the central nervous system. They have several cellular extensions, some of which are specialized to aid nutrient transfer called end feet. However, in the face of inflammation, astrocytes become reactive and can proliferate, hypertrophy, and increase matrix production. Astrocytes have characteristic filaments of glial fibrillary acid protein (GFAP), which serves as a specific cell marker. Immunostaining for GFAP is used for astrocyte identification and study gliosis. It is reported to increase within the first 7 days of implantation of invasive electrodes. However, the GFAP concentration may decrease over time following implantation.

Acute inflammation may decline as would be observed in a stab wound, but chronic inflammatory reaction eventually sets-in in response to foreign body effect. This involves reactive astrocytes and microglia. Activated microglia tries to phagocytose foreign material for degradation, and adheres tightly to the foreign material when it cannot degrade the foreign material. The eventual formation of a fibrotic avascular glial scar is a long-term immune response to invasive electrode. This leads to encapsulation of invasive electrodes, which is a protective response of the body to separate damaged areas from the other neurons, and to maintain the blood brain barrier [56]. However, this increases the distance from the electrode and neurons, increases impedance and cell death. Generally, this leads to significant loss in signal quality for neurosensing and neurostimulation [15]. Invasive electrode tethered to the skull appears to elicit greater inflammatory reaction than free-floating invasive electrode on the brain. This could be as a result of increased micro-motion of invasive electrode on the brain in tethered invasive electrodes as the whole brain moves and float in the cerebrospinal fluid [16].

Neurotrophicity

Neurotrophism is the prevention of neuronal death and neurotropism is the promotion of axonal growth after injury [62]. The cone electrode, also called the neurotrophic electrode, produced by Neural Signals Inc. achieves neurotrophism without neurotropism. Neurotrophic factors are inserted into the glass cone, which stimulates the growth of neurites through to interface with gold wires creating a

bridge between brain tissue and the electrode. The neurites are observed to become myelinated over the course of 3-4 months. Longevity has also been documented for this type of electrode with signals being recorded after implant at 15 months in monkey, 16 months in rat and 4 years in Human subject [32].

Other ways to improve neurotrophism may include the use of biopolymers. A number of studies have focused on polypyrole (PPy) which indicates that topographically modified surface of invasive electrode can enhance axonal and dendritic growth. Electrical stimulation through oxidized PPy has also been found to increase neurite length in rat PC-12 cells in vitro. However, PPy is not suited for long-term implantation because it may lose its electrochemical activity over time [63]. Poly 3,4 – ethylenedioxythiohene (PEDOT) was studied as alternative for chronic use. Preferential growth of neuron and high quality recording was observed on the coated area of standard acute Michigan probes coated with PEDOT/DCDPGYIGSR (DCDPGYIGSR is a bioactive peptide) [64,65]. Dexamethasone is a corticosteroid and a potent anti-inflammatory agent, incorporated on Michigan probes showed reduced gliosis and invasive electrode encapsulation [15]. Other possible anti-inflammatory agent for clinical use may include α melatonin stimulating hormone (αMSH), which inhibit nitric oxide production in microglia and thus controlling inflammation [66].

Other issues

Both MEG and MRI technology requires high sensitive magnetic sensors within super conducting shield, hence very heavy for wearing outside of clinical settings [34]. There are many EEG devices that can be used in real-life settings for long duration, however most are visually identifiable and discernible [10]. There are commercially available wireless EEG devices that capture data from 1 to 256 channels, and some of them are easy and convenient to put on. The feelings of sensors and the harness could be inconvenient, and relevant research is showing promise [46,52]. Usability and comfort are significant challenges to the potential for such technologies to be utilized in long duration BCI applications.

Processing of Brain Signals

For useful processing of brain signals towards BCI applications for diagnosis, prognosis, monitoring, feedback, and so forth, the brain signals captured through these sensing technologies must be processed by low-noise, high-gain amplification and filtering, removing artifacts from the signals, extracting features of interests, and classifying with intelligent and adaptive algorithms [67,68]. Special signal conditioning circuitry is typically required to enable the brain signals to be sampled, digitized and processed [69]. Typical signal conditioning would involve high input impedance buffer, low-noise amplification of brain signals, filtering through a band-pass filter of high order, and driving of signals to reduce common mode noise [20,70,71].

Removal of artifact from brain signals must be performed prior to reliably extract features for classification. As brain signals are small in amplitude, they are easily susceptible to various types of artifacts. For instance, EEG signals are strongly affected by different artifacts that may be ocular activity (eye blinking, fixations and saccades), muscle activity, power line interferences or heart beat activity [72]. It is important to efficiently suppress these artifacts so that a clean artifact free brain signals can be obtained for analysis. As it is not practical for a subject to avoid most of these artifact generation, such as eye blinks, eye movement or heartbeat, it becomes very crucial therefore to effectively remove these artifacts from the data before further analysis. The traditional approach to remove the eye blinks is to use the linear filters for certain frequency bands that belong to artifact range [73]. This however leads to significant loss of neurological activity, as there is always spectral overlap between neurological and artifactual phenomenon [74]. Another common practice for correcting the ocular artifacts (OA) is by using regression analysis [75]. Other methods with Principal Component Analysis (PCA) [76], Independent component analysis (ICA) [77-80], wavelet based denoising [76-78,81-83], Wavelet enhanced ICA (wICA) [84-86] and wavelet with higher order statistics [87] have also been proposed with varying degrees of success [88]. Jointly using statistical tools like Kurtosis, data improbability, linear trends, spectral pattern with the independent component scalp maps [89] and Kurtosis with Renyi's entropy [90] have also been used to identify artifacts. Furthermore, various adaptive algorithms have been developed to improve efficacy of artifact removal [91].

Feature extraction and classification of brain signals specifically depends on the neurological phenomenon to be analyzed, nature of episodes, characteristics relationships of source signals on applications, similarity matrices and correlations, entropy and other factors [92]. Classical patter classification algorithms can be applied for many types of applications [93]. However, due to varying nature of brain signals and continually changing interfacing characteristics, adaptive algorithms with learning sets are more practical [94]. A major application area for BCI is epileptic patient diagnosis and treatment with adaptive classification [95]. In addition to detection of such ictal episodes and Alzheimer's patient monitoring, algorithms have been proposed that utilizes analytics from phase synchrony of various brain lobes [96-101]. Recent findings of early detection of neurological disorders such as epilepsy, autism, and Alzheimer's disease as well as real-time monitoring of cognitive loads and collaborative learning show promise of BCI technologies as a viable medical tool of next generation [12,46,102-104].

Applications of Brain Activity Monitoring

Any type of effective BCI would require high spatial and temporal resolution for acceptability in clinical use [18]. The highly invasive nature and limited longevity of invasive electrode challenge its clinical applicability. However, there exist large number of invasive neural device that is Food and Drug Administration (FDA) approved with low incidence of complications such as the deep brain stimulation and the cochlear implant. Deep brain stimulation inserts electrode deep into the brain into the subthalamic nucleus for high frequency stimulation [21].

Invasive electrode can record neuronal activity and convert it to motor activity in a robotic prosthetic for amputees [53], limb paralysis and tetraplegia. Many cases of tetraplegia or locked in syndrome leaves the cognitive function largely intact. This means that a person is fully conscious and aware of the environment but has lost the ability to move the limbs. There are huge numbers of causes of tetraplegia including spinal injury, brain stroke, and amyotrophic lateral sclerosis [105]. The cerebral cortex contains movement signals, which could not be executed because of the loss of executive neural pathway or limbs. Invasive electrode records these signals, and algorithms are used to interpret the signals for an actuator to execute the action on an actuator [105]. Tetraplegic patients with complete loss of motor function usually have loss of sensory function, which leads to a loss of sensory feedback. In the design of a robotic prosthetic, feedbacks are

usually visual which could lead to aberrant neuroplasticity [53]. Sensory feedback into appropriate sensory cortex is desirable and has been attempted using thin film longitudinal intrafascicular electrode (tfLIFE) in amputees [106] utilizing existing peripheral nerve pathways or direct stimulation of the sensory cortex by intracortical microstimulation [28]. Less challenging tasks would include the reconstruction of cortical signals considered as intent to voice or writing electronically. Invasive electrode is also being studied for drug delivery channels using microfluidic channels in the device and may be an opportunity in neuropharmacology in conditions like severe epilepsy, brain injury and other localized organic brain disease [23].

Non-invasive brain signal monitoring has been established to identify sleep disorder and to monitor the depth of anesthesia. Besides, real-time monitoring of brain signals can allow detection, and even prediction, of ictal episodes for epilepsy patients [101]. Access to brain activity monitoring technology like EEG in various practical settings such as classroom, training session, testing facility and other safety-critical situations, could deliver a significant leap in identifying competent leaders and high performers for real-life stressful activities including those associated with emergency, medical and other crisis [12]. Along with healthcare, homecare monitoring of elderly people and children with developmental delays can be realized with low-cost brain signal monitoring solutions. In addition, the rising concern about brain injuries in many sports as the National Football League, as well as the collegiate and high school levels, would be an area that brain monitoring system could identify potentially harmful conditions of a player or athlete, and to allow medical personnel to diagnose these conditions prior to a point where irreversible damage is done. Advances in neural interface have also improved the understanding of the nervous system; the anatomy, physiology and concepts of neuroplasticity.

Conclusion

Rapid advancements in microelectronics and embedded systems have quickened development and improvement of many brain signal monitoring technologies. There are two primary approaches of signal acquisition for invasive electrodes. In one approach, signal of neuronal activities from action potential of individual neurons are collected from a layer inside the cortex where electrodes penetrate the pia mater and at some depth inside the cortex to reach the desired location (eg. Microelectrode, MEA). In the other approach, electrodes reside at epidural or subdural layer and provide information of synchronized neuronal activities by measuring the surface field potential or LFP (eg. ECoG). Both approaches can possibly be implemented with a single electrode or an array of electrodes. Currently available non-invasive brain signal monitoring techniques are EEG, MEG and fMRI. While MEG and fMRI requires highly sensitive magnetic sensors, thus limited to clinical settings, EEG provides a solution towards brain signal monitoring in natural settings. However, the spatial resolution of EEG is significantly inferior compared to MEG or fMRI. Miniaturized, long duration useable, and portable versions are being developed by many research groups, along with the research to develop new modalities for non-invasive brain sensing such as NIR for real-life monitoring. One can envision these types of technologies to be routinely worn by individuals in near future for long periods, that seamlessly collects, stores and smartly communicates neurological information along with associated physiological data in an autonomous fashion for the vital monitoring of patients with various neurological disorders, as well as for preventative, proactive monitoring of individual well-beings.

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