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TRENDS AND FUTURE PERSPECTIVES ON SENSING IN BRAIN MACHINE INTERFACES

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ABSTRACT

Brain machine interfaces (BMI) are rehabilitation tools in which neural functions, such as walking, talking, hearing and seeing are modulated through feedback that is triggered by either decoded external percepts or brain activities. Some of the major challenges of BMI as rehabilitation tools involve difficulties in physiological signal analysis. To overcome these challenges, signals as well as sensing devices that clearly distinguish various states in patients across time and condition are required. In sensing for BMI, characteristics like implantability, spatio-temporal resolution and invasiveness are essential. Sensing in BMI is required to either control perception to the brain or actuation from the brain. Hence, this review focusses on those that control neuro-motor functions by using brain activity to ameliorate, mitigate or restore bodily function in patients with disabilities. In addition, the review proposes future perspectives on sensing for BMI. Even with the surge in research on BMI, the major challenge still remains translating research to real-life applications. These transitions have mainly been hindered by limitations in sensing technology which this work provides more insight into. It is hoped that future BMI applications could adopt paradigms that combine metabolic and electrical activity sensors for acquiring brain responses in real-time. This increases spatio-temporal resolution; thus, improving information content and disease identification.

Keywords: Bio-signal processing; Brain machine interface; Deep brain stimulation; Feedback algorithms; Neural activity measurement.

1. INTRODUCTION

Brain machine interface (BMI) transduces brain signals to enable some form of communication between the brain and a machine – both machine and brain can take up the role of the transmitter and receiver. Fig. 1 depicts the bidirectional communication of an idealized BMI system. Generally, there are various ways BMIs can be classified: based on: its function, level of invasiveness, origin of neural signal and its design (Lebedev & Nicolelis, 2017). However, in this review more focus will be on the classification of BMI based on function. When classified based on functions, they can be broadly divided into two categories (Nicolelis, 2001). The first category is perception assistive BMI. These are devices that relay on sensory information by stimulating relevant regions of brains concerned with various perceptions like sound or vision s to mimic their neurological function. The second category are actuation assistive devices, which are devices that decode neural activity in real-time so as to control prosthetics, motor disorders, pain and other impairment or disabilities. Among the two groups, the former controls perception to the brain based on sensory information, while the latter controls actuation to a body part or prosthetics based on recorded neural activity from the brain.

Fig. 1. Idealized bidirectional brain–machine interface.

Both categories use electrical signals to relay sensory and actuation information respectively (Lebedev & Nicolelis, 2017). They can also be used to restore, reinforce and facilitate human sensory-motor functions (Chaudhary, Birbaumer, & Ramos-Murguialday, 2016). Advances in neuroscience have led to a surge in BMI research. However, the major challenge still remains translating research to real-life applications. These transition has mainly been hindered by limitations in sensing technology; unreliable algorithms for signal analysis and interpretation; and ineffective control strategies (Wu, Lance, & Lawhern, 2017). To address some of the challenges, proper

Fig. 2. Processing chain of perception assistive BMI

understanding of BMI sensing technology is required.

The major challenge to the analysis of physiological signals has been the choice of feedback signals and their signal acquisition technology. The sensing stage quantifies brain activity such that it can be used to control a prosthetic limb or to mitigate neuro-motor disorders. For effective neural recording ,cutting-edge techniques that access deep and distant regions of the brain are required (Ha et al., 2017). This has led to an upward trend in the development of miniaturized recording devices with high spatio-temporal resolution. A notable example of this is the encapsulated neural acquisition chip that records electrophysiological activities from the gyri and sulci of the brain (Ha et al., 2017). It provides a high spatiotemporal resolution, which could lead to having more insights into brain dynamics. Major breakthrough in understanding neurophysiological dynamics is dependent on advances in BMI data acquisition (Muraskin et al., 2017), because the first requirement towards achieving an efficient BMI detection algorithm is acquiring neural signals without compromising their quality. This is why various feedback signals are analyzed as well as signal acquisition techniques. The list is not exhaustive, nevertheless it presents the most prominent signal acquisition techniques in BMI applications. Several studies have reviewed BMI applications (Mudgal, Sharma, Chaturvedi, & Sharma, 2020), (Waldert, 2016), (Mohammed, Ahmad, Abdullahi, & Kabir, 2020). The work in (Mudgal et al., 2020), reviews the applications of BMI in different fields and practical issues related to usability of BMI. The review in (Waldert, 2016), possibilities and limitations of invasive and non-invasive methods to fully interface the brain. Further works have investigated on algorithms and paradigms and having objective methods to compare various BMI technologies (Mohammed et al., 2020). This work provides a new dimension by focusing on sensing techniques and feedback signals that are obtainable from the brain, excluding external signals. Due to the level of invasiveness required for internal signals, most studies have focused on external signals. In addition, the review proposes future perspectives on sensing for BMI.

2. PERCEPTION ASSISTIVE SENSING

These are signals that are used to help enhance sensory functions in patients with auditory, visual or any other sensory impairments. Stimulation is triggered using mainly signals external to the brain. This class consists of visual and auditory prosthesis like cochlear and retinal implants. Cochlear implants work by converting sound into patterns of electrical stimuli that are delivered using a collection of implanted microelectrodes to the auditory nerve fiberlying on the basilar membrane of the cochlea (Nicolelis, 2001). By substituting the percepts with sound and the neural system with the auditory nerve, Fig. 2 summarizes the processing chain of a cochlear implant; which is a typical example of a BMI that enhances percepts. Sound enhancing prosthesis were the first successful prosthesis. They were developed as early as the 19th century by Miller Hutchinson as hearing aids (Mills, 2011). Making them the earliest BMIs to be commercially available. In 2013, the Food and Drug Administration (FDA) approved the first retinal implant (Greenemeier, 2013). Like the cochlear implant, the retinal implant uses decoded captured images as control signals, which are then used to stimulate the optical nerve through a set of electrodes (Costa e Silva & Steffen, n.d.). The retinal implant uses a similar processing chain to the cochlear implants as shown in Fig. 2. With the retinal implants, the percepts is vision and the neural system to be modulated is the optical nerve (Niketeghad & Pouratian, 2019). Work on retinal implants is still at its early stages, and they have shown a lot of promise; however, they are still grappling with low resolution, making it difficult for blind patients to use it for daily living activities (Luo & da Cruz, 2016).

3. ACTUATION ASSISTIVE SENSING

These consists of the group of neural signals used to rectify, restore and ameliorate external bodily functions, mainly motor disabilities. Fig. 3 depicts a BMI using brain signals to control a prosthetic limb. Prosthetic limbs like this restore grasp and gait abilities to seriously disabled patients, who may be totally paralyzed or those with severe neuro-motor limitations. In restoring bodily functions, more neural information can be obtained using innovative approaches having high spatio-

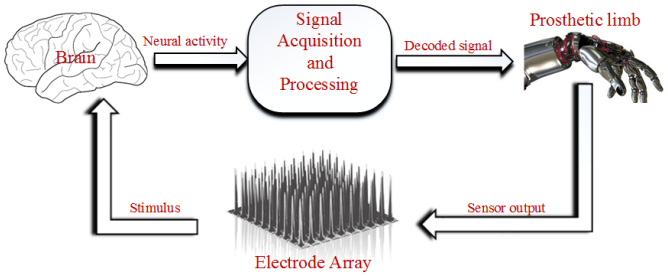

Fig. 3. Actuation assistive BMI using brain signals to control a prosthetic limb

temporal resolution or techniques measuring multiple brain activities (Muraskin et al., 2017). In terms of neural activity measured, this review broadly classifies them into two categories: electrical and metabolic activity. The following is a brief description of the various modalities used in obtaining electrical and metabolic activity from the brain.

3.1 Electrical Activity Sensing

Neuro-electrophysiology has been used in studying bio-electrical properties of brain cells and tissues. Notable among, was the revolutionary discovery by Hodgkin and Huxley in 1952, on the initiation of action potentials in squid axons which eventually led to a Nobel Prize (HODGKIN & HUXLEY, 1952). Later, there was the discovery by Hubel and Wisel in 1977, about how individual neurons contribute to visual processing (Hubel & Wiesel, 1977). These ground-breaking studies set the pace in neuro-electrophysiology. In order to extract useful information from neuro-electrophysiological signals, a good understanding of how these signals are formed at the neural level is required. Generally, neuro-electrophysiological signals represent the spiking behavior of a single neuron, a small neural ensemble and the mean potentials of a large neural ensemble. The larger the neural population, the higher the amplitudes as more neurons contribute additively to the signal.

Neuro-electrophysiological signals are used for various applications in clinical settings. Primarily, they have been used in brain-machine interfaces as feedback signals. In BMI, implanted devices are used to record and decode brain signals, which are used in controlling external machines, like prosthetic limbs (Hochberg et al., 2006). Additionally, electrophysiological signals are used in localizing areas where seizures begin in both medically tractable and intractable epilepsy (Staba, Wilson, Bragin, Fried, & Engel, 2002). They have been proven to be good markers for movement disorders such as Parkinson's disease (PD), essential tremor (ET) and dystonia (Little & Brown, 2012). Their use is extending to tracing neuropsychiatric disorders like obsessive compulsive disorder (OCD), dementia, attention deficit hyperactivity disorder (ADHD), Alzheimer's disease (AD), and schizophrenia (SZ) among others (Yener & Başar, 2013).
Fundamentally, feedback signals should be selected based on their level of invasiveness, resolution, signal content, and clinical relevance. The selection of signals will ultimately depend on the design of the entire system in relation to the signal processing capability available. The following sections give a brief description of the sensing techniques and signals obtainable by electrical activity in the brain.

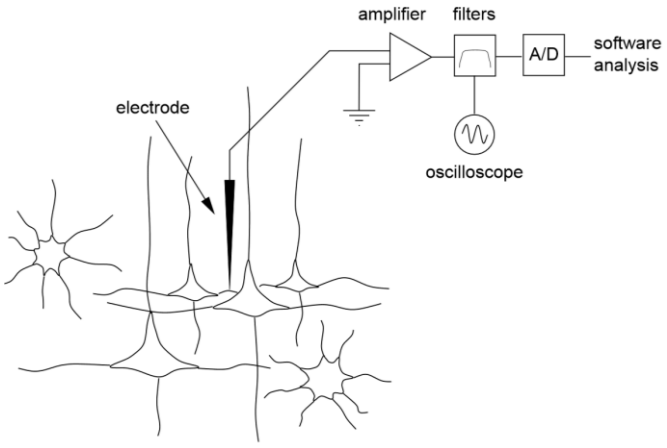

Fig. 4. The basic set-up for measuring and analyzing extracellular neural signals (Lewicki, 1998). The set-up shows the low noise amplifier (LNA), band pass filter (BPF) and analogue to digital converter (ADC).

3.11 Neuro-electrophysiological Recordings

Intracellular recording is the measurement of voltage or current within the membrane of a cell. This is done by inserting an electrode in the cell and a reference electrode outside the cell. This could be done using a current or voltage clamp (Romain Brette et al., 2008). In a current clamp, current is injected through the intracellular electrodes and the resulting amplified membrane potential is measured. Whereas the voltage clamp holds the membrane potential at a fixed value and the current flowing through the intracellular electrode is measured. The major techniques used in intracellular recordings are measurements of current, potential and conductance.
On the other hand, extracellular recording is the main method for measuring in vivo neural activity. For a single neuron, extracellular recording is achieved by placing an electrode close to the neuronal soma such that the firing rate of the neuron is measured by the number of spikes (Roman Brette & Destexhe, 2012). Extracellular recording has been more prevalent due to its ability to provide neuronal activity, coupled with its relative ease of use compared to intracellular activity. Aside from single neuron activity, research is growing in the study of how a network of neurons influences various functions like cognition, movement and perception. These studies have mainly used extracellular recordings using multi-electrode arrays (MEA). Extracellular potentials provide information consisting of high frequency spiking activity (> 500 Hz), which stem from a number of neurons within the immediate vicinity of recording electrode and are termed multi-unit activity (MUA). And the low frequency potentials consisting of local field potentials (LFP). Fig. 4 presents the conventional set-up for measuring extracellular activity from a neural population. An ideal measurement technique is required to be able to provide activity of single neurons, at the same time providing whole brain activity, within a microsecond time scale (Roman Brette & Destexhe, 2012); which might only be achievable by combining recordings from various techniques.

3.12 Unit Activity

Using sharp extracellular electrodes as in Fig. 4, action potentials are generally extracted from a single neighboring neuron (single-unit recording) or from an unknown population of neighboring neurons (multi-unit recording) (Gold, Henze,

Koch, & Buzsáki, 2006). These are mostly high frequency extracellular potentials (>500 Hz). Single unit activity is used in understanding how a neuron responds to specific stimulus or to understand correlation between various neurons. This has led to their use in providing insight into patterned activity within the subthalamic nucleus (STN) and globus pallidus internus (GPi) in relation to movement, cognitive processes and memory; making them potentially suited as biomarkers for use in closed-loop deep brain stimulation (DBS). DBS is a tool used to mitigate pharmacologically intractable neurodegenerative diseases such as Parkinson's disease (PD), tremor and dystonia. As such, closed-loop DBS uses feedback signals to track changes in patient's condition and correspondingly adjust stimulation so as to improve their condition. Closed-loop DBS is an instance of BMI. Nevertheless, they are hindered by recalibration (due to drift in neuronal properties), need for precision on target neuron and unreliability of recording over extended use (Little & Brown, 2012). Single neuron recordings represent certain movement features, nonetheless, they have higher sampling rate requirements, degradation at the neuron-electrode interface and difficulty in maintaining recordings from the same neuron for extended periods of time. However, the difficulty in maintaining recordings has been as a result of the size of recording electrodes, which mostly picks up neuronal ensemble activity as against the required single unit activity (Buzsáki, 2004). This has necessitated the need for additional processing unit such as; spike sorting to aid in extracting single unit activities from multiunit activities. Compared to other neuro-electrophysiological signals, unit activities are useful in brain-machine interfaces (BMI) applications, since high spatial resolution is required. Spikes have been found to show a clear relationship to movement and behavioral functions as highlighted by their application in BMI for prosthetic limbs. This has led to their use as biomarkers for regulating stimulation in closed-loop DBS (Rosin et al., 2011).

3.13 Local Field Potentials

LFP are low frequency (<500 Hz) extracellular potentials obtained from sampling alocalized population of neurons. LFPs can simply be measured with a standard electroencephalography (EEG) amplifier connected to the implanted DBS electrode, and are generated by summated postsynaptic potentials resulting from excitation in basal ganglia and cortical neurons(Priori, Foffani, Rossi, & Marceglia, 2012). Unlike unit activity, they tend not to drift over time which makes them more reliable and stable (Buzsáki, 2004).Because of their population-based nature, they are more informative, due to their time and frequency response; and offer a better trade-off between high spatial resolution (common in unit activity) and high spatial scale (common in global field potentials) than other neuro-electrophysiological signals. Another advantage of localized population of neurons is the long-term experience acquired by researchers in signal processing for EEG-like signals researchers have, particularly LFPs. Fig. 5 illustrates the region where LFP recording can be obtained. Also, LFP processing algorithms can be easily implemented on microchips, and are therefore ideal for use in implantable devices. Since LFP processing microchips have been adopted in several studies, using LFP means no additional work or procedures to be undertaken. This makes them ideally suited for many applications requiring neural signals for feedback. As biomarkers for closed-loop DBS, current evidence supports the hypothesis that LFP activity changes in response to the patient's clinical state. Basal ganglia LFPs oscillate in several frequency bands, ranging from; very-low frequencies (2–8 Hz), beta frequencies (8–20 Hz), alpha (20–35 Hz), gamma (60–80 Hz), and very-high frequencies (250–350 Hz). The most studied and debated LFP oscillations are beta frequencies because they seem to reflect the patient's motor state. Changes in beta LFP activity mainly reflect basal ganglia responses to dopamine and correlate with motor performance.

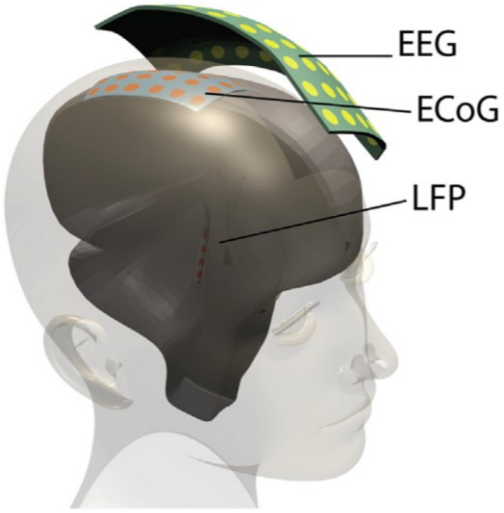

Fig. 5. Candidate neuro-electrophysiological signals and their recording sites (Hebb et al., 2014).

As suggested, LFP have been found to be the prime candidates for closed-loop DBS. This is so, even though the exact mechanisms of DBS are still under debate, ample evidence shows that LFP oscillations in patients with Parkinson's disease and other neurological disorders requiring DBS are specifically modulated by DBS (Urrestarazu et al., 2009). Notwithstanding, LFPs have their limitations, some of which are listed below:

- There is evidence that LFPs correlate closely with the individual patient's motor status, but correlation across patients is yet to be established (Little & Brown, 2012).
- Recent studies suggest that other activities like cognitive and behavioural functions might modulate LFP (Urrestarazu et al., 2009).
- Abnormal oscillations reflect some sort of clinical impairment in patients, but direct relationships are yet to be established (Kühn, Kupsch, Schneider, & Brown, 2006).
- Conversely, there is no correlation between beta band LFP and neuro-motor scores like the unified

Parkinson's disease rating scale (UPDRS), making some studies to downplay its importance (Kühn et al., 2009).

Generally, LFP has a relatively better correlation with neuro-motor symptoms compared to other neuro-electrophysiological signals. Various clinical studies have employed it as a biomarker (Little et al., 2013)(Afshar et al., 2012)(Camara et al., 2015), and numerous computational studies have been concerned with its manipulation in subjects (Mohammed, Zamani, Bayford, & Demosthenous, 2017)(Mohammed & Demosthenous, 2018)(Grant & Lowery, 2011)(Santaniello, Fiengo, Glielmo, & Grill, 2011)(Rosenblum & Pikovsky, 2004)(Omel'chenko, Hauptmann, Maistrenko, & Tass, 2008)(Lysyansky, Popovych, & Tass, 2011)(Franci, Chaillet, & Pasillas-Lépine, 2011).

3.14 Global Field Potentials

These are activities from a much larger population of neurons than LFP. Like LFPs, EEG measures the summed electrical activity of many neurons and is measured with electrodes at the surface of the scalp; though at a larger scale. Fig. 5 depicts the recording sites for EEG and Electrocorticography (ECoG) which are examples of global field potentials. From Fig. 5, it can be seen that EEG are subject to filtering due to propagation through various media such as the cranium, dura mater, cerebrospinal fluid and other surrounding tissue (Roman Brette & Destexhe, 2012). Due to this frequency filtering, action potentials are severely attenuated and are not visible on EEG electrodes.

In addition, low frequency activities such as synaptic potentials dominate EEG signals, since they can propagate over large distances within the extracellular space. EEG recordings provide average activities of neurons on the order of $10^5 – 10^8$ (Rowland, Breshears, & Chang, 2013), this inhibits both their spatial and temporal resolution. On the other hand, ECoG can be used to overcome some of the shortcomings of EEG. ECoG measurements are made on the surface of the cortex as is shown in Fig. 5, which results in less filtering compared to EEG which is made on the scalp. Like EEG, ECoG measures the summated electrical activity of many neurons, to be precise, it uses the summation of between $10^2 – 10^3$ neurons (Rowland et al., 2013). This enables ECoG to record frequencies up to 200 Hz compared to the less than 70 Hz present in EEG (Schwartz, Cui, Weber, & Moran, 2006). Thus, EEG and ECoG literally make the same measurements, though EEG signals have poorer spatio-temporal resolution due to filtering by cortical tissue and their large coverage area.

In BMI, higher frequency contents in signals mostly leads to more relevant information for decoding patient state and intentions; which are necessary for BMI control (Schalk & Leuthardt, 2011). Due to the lower frequency-specific information content of EEG compared to other neuro-electrophysiological signals, their long-term use as biomarkers may be unsuitable. Nevertheless, they relatively have a higher spatial scale compared to the other signals since they cover the whole brain; making them suitable for acquiring more general fluctuations in frequency information across the brain. This property makes them ideally suitable as complementary signals in BMI applications. As a result of this, EEG have found application in responsive stimulation for epilepsy. Their adoption in epilepsy makes them an option for PD applications, since epilepsy is a neurological disorder impairing movement and other behavioral functions just like PD.

3.2 Metabolic Activity Sensing

In BMI, hemodynamic or neuro-transmitter response could be used in obtaining vital brain information. In neuro-motor disorders, excitation and inhibition of neuronal signals occur as a result of stimulation and improvement in conditions. In addition, other secondary effects are, blood flow changes, modulation of neurotransmitters, neurogenesis and a host of other metabolic activities (Hess, Vaillancourt, & Okun, 2013). This makes the investigation of metabolic activity for BMI important.

For hemodynamic response, blood releases glucose to active neurons at a higher rate than in the area of inactive neurons (Nicolas-Alonso & Gomez-Gil, 2012). The glucose and oxygen released to the blood stream results in an increase in oxyhemoglobin in the veins around the active region. In DBS, hemodynamic changes in PD patients can serve as good biomarkers since DBS and PD induce cortical hemodynamic changes in patients (Bick et al., 2017). These changes can be detected by methods such as functional magnetic resonance imaging (fMRI), diffusion magnetic resonance imaging (dMRI) and near infrared spectroscopy (NIRS). Like in hemodynamic responses, the use of techniques that measure neuro-transmitter response is pertinent because most neuromotor disorders like PD, results in degeneration of cells that use dopamine as neurotransmitters (Schiff, 2012). Monitoring dopamine traces from cerebral metabolites have been reported (Little & Brown, 2012), but miniaturization of chemical analysis is a major barrier.

In addition to monitoring neurotransmitter and hemodynamic responses, responses to specific molecules are measured using optical micro-imaging techniques mostly by using fluorescence measurements. Recent advances in optical imaging techniques have led to single-cell resolution in functional neuroimaging which uses a two photon microscope (Helmchen & Denk, 2005). Understanding pathological brain processes down to the single neuron level is necessary towards harnessing the ability of closed-loop DBS as well as BMIs to restore bodily functions. The advantage optical approaches have over other methods is that they have high spatial localization and are relatively less invasive (~ 1 – 2 mm in depth) compared to other methods (Takehara et al., 2015). However, their major shortcoming is their low temporal resolution compared to neuro-electrophysiological methods. This is partly due to their high requirement for signal processing and data analysis (Schultz, Copeland, Foust, Quicke, & Schuck, 2017). Table I presents a summary of the major methods used in analyzing and obtaining

metabolic activity from the brain that can be used in BMI applications.

3.21Fluorescence Measurements

Fluorescence measurements have a distinctive response to the presence of specific molecules like sodium, potassium or calcium. Fluorescent measurements of neuronal activity can be classified into two categories: those that are sensitive towards membrane voltage and those that detect changes in intracellular calcium concentration (Schultz et al., 2017). Sensors sensitive to membrane potentials produce relatively small signals in response to action potentials. Currently, calcium sensitive sensors are orders of magnitude more sensitive than sodium or potassium sensitive sensors. In principle, initiation and propagation of action potential can give rise to about a hundred times higher calcium concentration that under rest (Berridge, Lipp, & Bootman, 2000). This can be used to measure active and inactive neurons in the brain.

3.22Near-Infrared Spectroscopy (NIRS)

NIRS uses optical spectroscopy based on infrared light to quantify changes in cerebral metabolism due to neural activity. Infrared light penetrates the human skull up to a depth of about 1- 3 cm below the skull (Hong, Ghafoor, & Khan, 2020). This enables NIRS to measure concentration of oxyhemoglobin based on light attenuation (absorption and scattering)(Alt et al., 2017). The shallow penetration of light makes it not very ideal for applications that monitor biomarkers in deep regions of the brain. Nevertheless, it is a promising diagnostic tool to investigate neurovascular coupling, for example in epilepsy to develop novel early seizure detection algorithms, because vascular changes occur about 100 milliseconds after the associated neural activity. Which is an acceptable temporal resolution for BMI applications (Coyle, Ward, & Markham, 2007). In addition, it has a spatial resolution of within 1 cm. The major advantage of adopting optical modalities like NIRS and fluorescence measurements in recording neural activity is their high specificity, which will go a long way in facilitating artefact free BMI implementations. For example, NIRS has been used in DBS patients by Sakatani and colleagues (Sakatani, Katayama, Yamamoto, & Suzuki, 1999). The finding suggested that therapeutic benefits were reflected by changes in oxyhemoglobin levels in the prefrontal cortex. Despite its bulkiness, NIRS has been proposed as a suitable measure of neuronal activity due to its ability to accurately quantify neuronal activity which is reflective of symptom severity and has been proposed as a candidate signal to adjust the parameters of DBS in a closed loop configuration (Morishita et al., 2016). Applications utilizing this technology for BMI is still at infancy. Thorough studies using an acceptable number of patients that produce encouraging results are required, so as to establish its feasibility.

3.23Magnetic Resonance Imaging (MRI)

MRI is an emerging technology for observing neural activity in the living brain. It has tremendous potential for use in applications like blood-oxygen-level-dependent (BOLD) functional magnetic resonance imaging (fMRI), which is a non-invasive method for monitoring brain functions (Muraskin et al., 2017). Like NIRS, fMRI is a measurement based on

TABLE I. COMPARISON OF POSSIBLE FEEDBACK SIGNALS AND SENSING TECHNIQUES FOR BMI (ADAPTED FROM (Mohammed, Bayford, & Demosthenous, 2018)).

Electrical Activity Measurements	**Spike** (Gold et al., 2006), (Buzsáki, 2004), (Rosin et al., 2011)	**LFP** (Urrestarazu et al., 2009), (Kühn et al., 2006)	**ECoG/iEEG** (Rowland et al., 2013)	**EEG** (Schwartz et al., 2006), (Schalk & Leuthardt, 2011)	
Activity Measured	Unit activity	average potential of a localised neural population	cortical or intracranial activity	Electrical activity from scalp	
Temporal Resolution	< 1 ms	~1 ms	~3 ms	~50 ms	
Spatial Resolution	~ 50 µm	~0.5 mm	~1 mm	~10 mm	
Level of Invasiveness	Invasive	Invasive	Minimally invasive	Non-invasive	
Practicability in BMI	Implantable	Implantable	Implantable	Bulky, but cheap	
Metabolic Activity Measurements	**Fluorescence Measurements** (Schultz et al., 2017), (Berridge et al., 2000)	**NIRS** (Alt et al., 2017), (Sakatani et al., 1999)	**fMRI** (Muraskin et al., 2017), (Fouragnan et al., 2015)	**FSCV** (Lee et al., 2007), (Chang et al., 2013)	**Intracranial dialysis** (Robinson et al., 2003)
Activity Measured	Ca^{2+}, Na^{+} or K^{+} concentration in the brain	Concentration of oxyhemoglobin	blood-oxygen-level and molecular displacement of water	Concentration of neurotransmitter (dopamine)	Concentration of neurotransmitter (dopamine)
Temporal Resolution	~30 ms	< 1 s	~1 s	~1 s	~1 s
Spatial Resolution	~ 10 µm	~ 5mm	~1mm	~ 30 µm	~ 200 µm
Level of Invasiveness	Invasive	Non-invasive	Non-invasive	Invasive	Invasive
Practicability in BMI	Implantable (with very high data analysis cost)	Bulky	Bulky (a major hindrance is DBS devices are still MR conditional)	Bulky (with high specificity and selectivity)	Bulky (with high specificity and selectivity)

hemodynamic changes, and it offers a spatial resolution in the millimeters range. It has been shown to offer tremendous insights into the underlying dynamics of the human brain (Fouragnan, Retzler, Mullinger, & Philiastides, 2015). In addition, understanding the underlying mechanisms can give more insight as to why different patients' brains respond differently to similar levels of stimulation.

Aside from fMRI, the complex activity in the white matter of the brain can be captured with great detail using diffusion magnetic resonance imaging (dMRI) (Hagmann et al., 2006). It captures the molecular displacement of water within a voxel. This is used to deduce the location and direction of white matter tracts based on the directional diffusion of water. Changes in white matter fiber tract have been used to understand the internal working of the brain. The work in (Muetzel et al., 2008), confirmed that changes in white matter fiber tract connection correlated with subject performance in specific tasks in healthy patients.

3.24 Fast Scan Cyclic Voltammetry (FSCV)

FSCV is a voltammetry technique that applies a linearly varying potential through carbon fiber microelectrodes (CFM), resulting in redox chemical reactions around the electroactive molecules (Lee et al., 2007). The concentration of analytes is measured by the magnitude of evoked current peaks to the redox reaction at the electrode surface. The relationship between the applied voltage versus the resulting current provides a chemical signature for the presence of certain neurotransmitters or analytes. FSCV detection is mainly limited to electroactive analytes; electroactive molecules like dopamine (a biomarker for PD), adenosine (a biomarker for sleep), and oxygen (which signifies the presence of anoxic brain injuries). The major limitations of FSCV are its bulkiness and that the lifetime of CFM is a few months, which restricts the application of FSCV detection to intraoperative approaches. For closed-loop DBS, using an anesthetized rat model, the Mayo Investigational Neuromodulation Control System (MINCS) in (Chang et al., 2013), was interfaced to FSCV to wirelessly regulate stimulation as a proof-of-principle test for closed-loop DBS using neurochemical signals for feedback.

3.25 Intracranial Micro-dialysis

Micro-dialysis is the most commonly used method to measure the chemical concentration of analytes in the brain (Robinson, Venton, Heien, & Wightman, 2003). It uses a dialysis probe that penetrates very small molecules in the brain. The brain is supplied with artificial cerebrospinal fluid, the quantity of molecules that diffuse into the probe and the dialysate are collected and analyzed off-line. Its spatio-temporal resolution is not excellent because a certain amount of dialysate has to be collected before any analysis can be done; which impedes time resolution. However, it has a very high degree of chemical selectivity and sensitivity. Due to its poor temporal resolution, microdialysis can only be used to measure long term changes in analytes or neurotransmitter for use in closed-loop or BMI applications. Basically, its sensitivity and selectivity make it suitable for applications like home-based monitoring of PD patients. This could go a long way in reducing the frequency of face-to-face visits for patients with prosthesis or neuro-motor disorders. Table I summarizes some of the characteristics of various feedback signals that are suitable for BMI applications. In Table I, characteristics such as sensitivity and accuracy are not presented, since they change with application as well as the adopted feedback algorithms.

3.3 Electrical versus Metabolic Activity

For effective neural recording, cutting edge techniques that access deep and distant regions of the brain are required (Ha et al., 2017). These could lead to more insight in brain dynamics. Nonetheless, of equal importance are techniques that have spatial coverage. A major breakthrough in understanding neurophysiological dynamics is dependent on advances in neural signal acquisition (Muraskin et al., 2017). This is the first requirement towards achieving efficient BMI systems.

Changes in the bio-chemical environment within the brain can be representative of intended actions and actual actions in patients. These characteristics make metabolic activity sensing suitable for quantifying neural activity. Notable example of techniques that measure bio-chemical activity are, NIRS, fMRI, intracranial dialysis, FSCV and fluorescence measurements. The use of metabolic activity as biomarkers have been investigated in (Morishita & Inoue, 2017). Their major shortcomings are safety concerns like MRI compliance and metal artifacts. However, some other metabolic activity sensors such as NIRS are not affected by metal artifacts, but have relatively poor temporal resolution compared to electrophysiological activity. Their size is a major impediment towards attaining fully implantable BMI systems. Generally, apart from sensitivity to metal artifacts in fMRI, metabolic activity offers many advantages compared to electrical activity recording, notably: absence of electrical noise, simultaneous imaging of a large number of neurons and selective recording from genetically-targeted regions of the brain (Kim & Jun, 2013). Their high signal to noise ratio, specificity and selectivity can go a long way towards facilitating artefact free BMI systems.

For electrical activity, information content is dependent on spatio-temporal resolution, with EEG and single unit activity on the extremes of the spectrum: EEG has the highest spatial scale and the least temporal resolution, while single unit activities have the highest temporal resolution and the least spatial coverage. LFP and ECoG offer a compromise in terms spatio-temporal resolution. Combined with their long-term stability at the electrode-tissue interface, this makes them very attractive feedback signals for applications in BMI (Little & Brown, 2012). To use them as universal feedback signals, the valid question is how informative are they compared to other neuro-electrophysiological signals? It is thus evident that the choice of feedback signals for BMI seems to be application dependent.

4 FUTURE TRENDS IN SENSING FOR BMI

BMIs are rehabilitation tools in which neural functions are modulated through feedback that is triggered by either decoded external percepts or brain activities. To facilitate implementation of BMI, a wide range of neural signals that could be obtained using various signal acquisition techniques are required. Neural activity measurements consisting of metabolic and electrical activity are the preferred choice for use as feedback signals. Metabolic activity measurements are more selective, specific and quantifiable than electrical activity measurements. On the other hand, electrical activity has a faster response than metabolic activity. Of all electrical activity measurements, LFP has the optimal trade-off in spatio-temporal resolution as well as stability. This makes it a prime candidate for non-invasive BMI.

The main aim of sensing in BMI is to provide sufficient information to the machine attached to the human brain, such that the patients' use of bodily parts are improved. Prosthesis rejection is a major challenge in state-of-the-art BMI devices. This has mainly been as a result of poor feedback signals. Prosthesis should be biologically and sensorially implanted in the body to ensure better integration (Stephens-Fripp, Alici, & Mutlu, 2018). A number of studies have investigated the use prosthetic device for every day activity (Clemente, D'Alonzo, Controzzi, Edin, & Cipriani, 2016), (Antfolk et al., 2012). However, most of this have been done using an external computer under laboratory conditions. Translating research to real-life applications has been a major challenge of BMI applications. These has mainly been as a result of inadequate data acquisition and poor feedback signals (Wu et al., 2017). To obtain more useful information, BMIs should incorporate external and non-invasive sensing modalities such that a more comprehensive sensory information is obtained. This can be obtained by utilizing changes in temperature, vibration, mechanical pressure to augment other internal measurements obtained either from electrical and metabolic activity. Using, this kind of approach, simple feedback strategies can be used to implement BMI systems. Which could make the systems less computationally intensive and more suitable for chronic application.

5 RECOMMENDATIONS

If purely internal signals are required, BMI applications can adopt effective paradigms that combine both metabolic and electrical activity sensors for acquiring brain responses in real-time which increases spatio-temporal resolution. This leads to better identification of disease and non-disease states in patients, as the level of information content is strictly dependent on spatio-temporal capabilities of the sensor. This complementary approach takes advantage of the best of both worlds: the fast response rate of electrical activity, and the slower more specific, selective and qualitative sensing offered by metabolic activity. The complementarity of sensing electrical and metabolic activity have found application in brain machine interfaces (BMI) (Muraskin et al., 2017), (Jorge, van der Zwaag, & Figueiredo, 2014). Adopting completely internal sensing leads to more practicable implementations that are non-invasive and less cumbersome.

6 CONCLUSION

Based on this review, it is clear that the major challenges of physiological signal analysis are: sensing devices and feedback signals. In BMI, feedback signals are required that clearly distinguish signals for different actions and intentions. These signals should be consistent across time and representative of various activities in subjects. Nevertheless, for this to be implemented fully, sensing devices that are implantable and non-invasive, as well as with optimal spatio-temporal resolution are required. By blending the right sensing modalities, BMIs have the potential to achieve the desired performance levels without impeding the patient's quality of life.

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