BRAIN-COMPUTER INTERFACES
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ARTICLE

A Functional BCI Model by the P2731 working group: Physiology

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ABSTRACT

The development of Brain–Computer Interfaces (BCIs) requires specialists in various fields, including engineering, computer science, medicine and neuroscience. Each of these disciplines possesses a specific and sometimes differing terminology, which creates obstacles to mutual understanding and research collaboration. The IEEE P2731 working group aims to improve communication among BCI researchers by developing a functional model and standard glossary that can be used in all relevant fields. This article describes the anatomical regions of the brain and physiological processes commonly used by BCI applications. It serves as an introduction to neurophysiology for engineers and other non-specialists, and it offers background to articles on the IEEE P2731 Functional Model and Glossary available elsewhere in this special issue.

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1. Introduction

The goal of a Brain–Computer Interface (BCI) is to detect, interpret and apply signals generated by a human brain. Depending on the system configuration, these signals can be used for scientific inquiry, for self-awareness, or for 'useful commands' when linked to actuators, physical or virtual prostheses which are also known as effectors [1]. For the purposes of this paper, the brain is considered a functional component in an engineered system, namely a BCI. Thus, the role of cerebral activity in general physiology, namely maintaining the human body, is beyond this paper's scope. The brain contains a network of functional regions which communicate to maintain life, but a BCI relies on the brain's response to a repertoire of stimuli, some of which are generated to control virtual or physical actuators. The stakes in mental engineering are high. BCI is often used as a scientific probe, but it also supports practical applications which may provoke profound social change. BCIs support a large range of objectives, and their users include scientists exploring the nature of cognition, marketers trying to influence consumer decisions [2], computer game developers [3], and medical, industrial and military organizations aiming to deploy thought-controlled machines in their respective domains

Indeed a living brain is essential to a BCI, but end-users of a well-designed system can treat the brain as a black box. A BCI operates on the principle that brains generate signals which can be detected through sensors attached to interpretive machinery. For nonscientific purposes, as long as equipment is properly used, what matters is the detectability and consistency of signals rather than the organism producing them.

This paper aims to introduce the physiological foundations of BCIs to developers with non-medical backgrounds. Its specific context is the BCI Functional Model developed by the IEEE P2731 working group to which the authors belong. We have already noted the diversity of disciplines contributing to BCI's expansion. Our committee is developing a standard glossary for BCIs that can be beneficially adopted by all users. The Standard Glossary needs a common framework of reference, and the P2731 Functional Model, which is the subject of this special issue, provides that framework by segmenting BCI systems into a series of modules. Needless to say, the human brain does far more than participate in BCI applications, but the field could hardly progress without contributions from neurophysiology. This paper aims to introduce the elements of neurophysiology most relevant to BCI-based applications.

A key challenge in BCI research is to identify how, where and why the brain generates the signals recorded by sensors. Accurate models of perception, imagination and other mental operations improve the engineering of BCI systems by enabling transducers – the topic of a subsequent paper in this special issue – to more

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accurately extract targeted neural activity from the variety of signals generated by the brain and surrounding tissues. Similar to psychology – discussed in 'A Functional BCI Model by the P2731 working group: Psychology' within this special issue – considerable ambiguity remains in neurophysiology, and many specifics of how the brain operates are unlikely to be explained in the near future. Current progress often results in more, not fewer, questions, and promising avenues of research have technical and ethical limitations. Theories of mental operation are complicated by the discovery that a single physiological substrate is rarely responsible for the phenomena observed in brain operation.

While BCI systems have contributed to our knowledge of the brain, they should be considered a subset of the tools available to study the organ of thought. As its name states, BCI seeks to interface with the brain, and a useful interface establishes a safe, persistent relationship. BCI requires neural probes, but the most accurate tools for probing brains – surgical implants of electrodes – are medically dangerous because they involve materials that react with neurons and vital supporting tissues [4–7]. Consequently, though they can achieve spectacular results over short periods, implanted electrodes are limited to rare cases of where therapy requires them. However, unprecedented progress in materials science, particularly in the fabrication of adaptable, biologically compatible probes, is expanding the safety zone for brain interfacing, and it is likely that techniques which are currently unsafe or unreliable will become commonplace in the future [8–10].

Advances in safety are paradigmatic of BCI's rapid evolution. In approximately a century since its discovery, brain sensing and recording technology has made progress that was unimaginable in previous eras and that has nearly kept pace with imagination during our own. The rate of change in BCI, and the capacity of engineers to create boundary-breaking components, makes it difficult to categorize BCI's elementary tools, methods and data formats. The P2731 Glossary and Functional Model attempt to remedy this situation, and the remainder of this paper describes the role of physiology in this developing IEEE standard.

The paper is organized as follows. Section 2 discusses the cerebral structures most exposed to BCI, and thus by no means should be considered a comprehensive introduction to cerebral anatomy. Section 3 describes how the sensors most commonly used in BCI relate to cerebral structures. Brains produce myriad signals, and Section 4 describes the subset most commonly used in BCI. Section 5 covers recent advances in neurophysiology that may one day support more advanced BCI applications. Section 6 explains physiological impediments to establishing a reliable cerebral interface, and Section 7 offers our working group's conclusions about the role of physiology in the P2731 Functional Model.

2. Cerebral Physiology

2.1. Gross anatomy of the brain

If we expose a brain, the visible surface is known as the cerebral cortex (Figure 1). The cerebral cortex is the outer surface of the cerebrum, which in turn contains numerous internal structures, and partially encloses the cerebellum, which protrudes visibly from the lower rear of the cerebrum near the brainstem. For brevity, our discussion will focus on the cerebral cortex because it informs the nomenclature of electroencephalography (EEG), which is the most widely used technique to record brain activity in nonscientific BCI applications. Also, a considerable amount of processing occurs within the cerebral cortex, including much of the mental activity considered uniquely human, though we must emphasize that the cerebral cortex works in concert with the brain's many parts. When necessary, we will introduce non-cortical features to clarify the principles embodied in the P2731 Functional Model.

Like other parts of the human body, the cerebral cortex is lateralized, that is, it possesses complementary sides. Even though the brain is not a sphere, by convention its sides are called the left and right hemispheres. One hemisphere is designated dominant, and this is visible in its contralateral control of hands. People with a dominant left hemisphere are right-handed, that is, it is easier to acquire fine motor control with

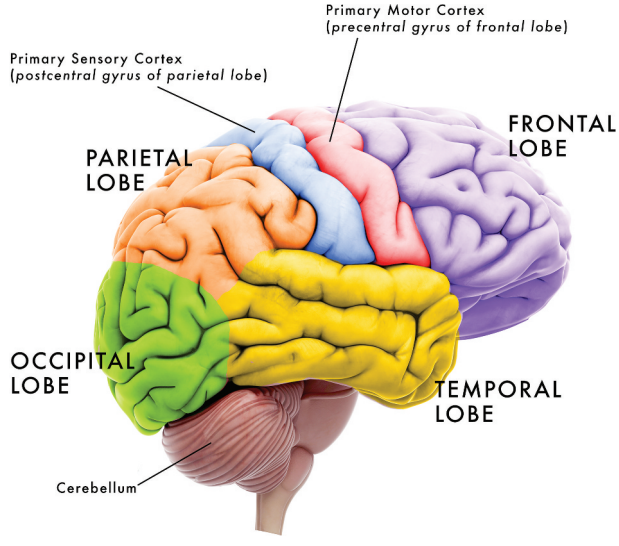

Figure 1. Gross (visible) anatomy of the human brain. [License: Shutterstock] .

their right hand. The opposite is true of people who have dominant right hemispheres. The neural organization that makes this possible is explained below.

The hemispheres are divided by the great longitudinal fissure which runs from the front to the back of the head, but a thick tract of flesh called the corpus callosum crosses the fissure. The corpus callosum contains nerves and other tissues that facilitate inter-hemispheric communication, and it enables the seemingly symmetrical hemispheres to perform specialized functions. Defects in the corpus callosum usually cause pathological symptoms, but some individuals who lack one show few effects. Even more surprising are cases of people who live with only one hemisphere [11]. This situation reflects an important consideration for BCI design: brains are highly adaptable. The brain's adaptability works to the advantage of BCI, for instance in human-machine teaming, but it also creates ambiguities in BCI system design because mental operations vary among individuals.

2.2. Anatomic organization of the cerebral cortex

An intact brain displays four primary structures: the frontal, temporal, parietal and occipital lobes (Figure 1). Brains may appear incoherent at first glance, and there are considerable differences among individuals due to age, health, gender, body mass and development factors [12,13]. Nonetheless, cerebral lobes possess enough regularities in the general population to identify them, and researchers periodically develop new approaches to defining cerebral regions with domain-specific accuracy [14,15]. Each lobe of the cerebral cortex forms a section of one hemisphere, and, though they mirror each other's appearance, the left and right sections often perform distinct tasks within the lobe's field of operation. Thus, though the brain contains eight visible sections, the lobes are named as singular structures across the two hemispheres. The rift that separates the left and right hemispheres has several names: the cerebral fissure, the great longitudinal fissure, the interhemispheric cerebral fissure and the median longitudinal fissure. Lobes communicate with their counterparts via the corpus callosum, and they connect to other regions of the brain and the spinal cord over thinner channels of nerves.

Figures 2 and 4 name the primary gyri and sulci, the ridges and grooves that give the brain its convoluted appearance. Most lobes are separated by a prominent sulcus which may extend for centimeters. Convolutions increase the surface area of the cerebral cortex, and, as a consequence, much of the functional surface of the brain is folded into sulci beneath its visible surface.

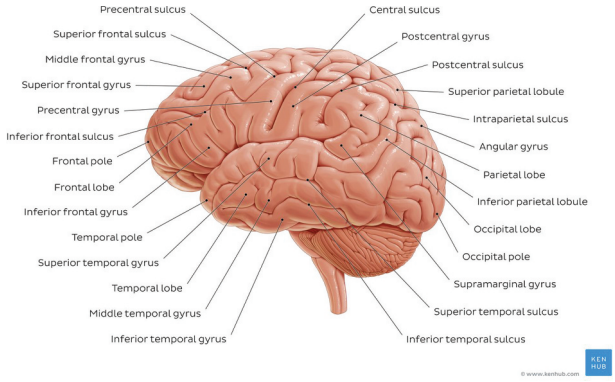

Figure 2. Lateral view of the brain [License: Kenhub] .

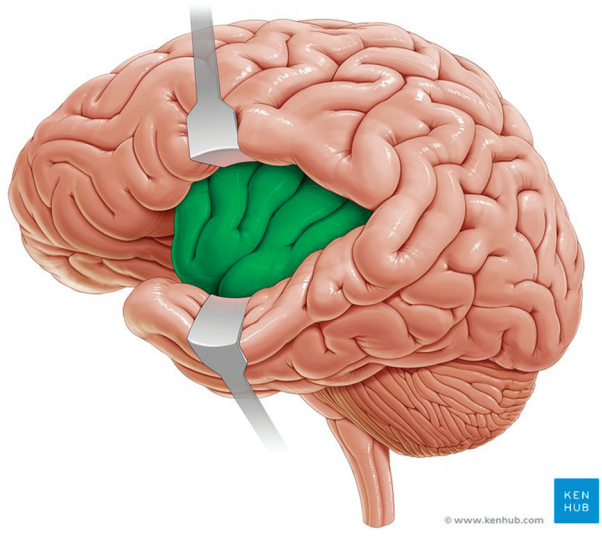

Figure 3. The insular cortex exposed [License: Kenhub] .

A notable sub-structure is the insular cortex, or insula, which is sometimes called 'the fifth lobe' as depicted in Figures 3 [16].

The anatomical organization of the cerebral cortex has consequences for BCI because cortical signals are more or less accessible depending on their location on a gyrus or sulcus and their position under the skull. Some signals are relatively easy to record while others require surgery, modified sensor geometry or large-scale equipment. Note that there may be significant differences in the cytoarchitectonics (or cellular organization) of individual brains which have no outcome on mental ability. As the following examples demonstrate, the three levels of gross cerebral anatomy – hemisphere, lobe and cortex – correspond to mental operations that are relevant to BCI.

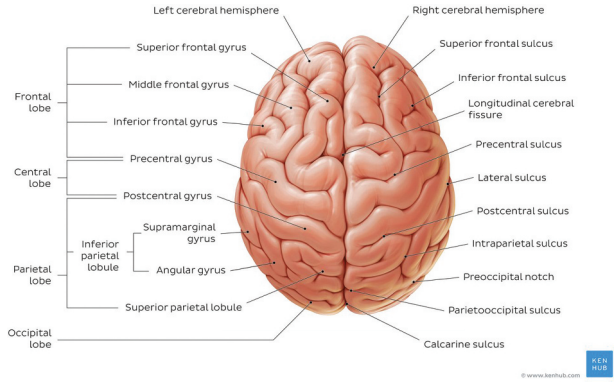

Figure 4. Dorsal view of the brain [License: Kenhub] .

Table 1. General functions of cerebral lobes.

Region	Purpose
Frontal lobe	Executive functions including planning and decision making, attention, error correction, motor processing and control of voluntary movement [20]
Parietal lobe	Somatosensory (bodily) sensations, selective attention to stimuli, visual processing, proprioception, bodily coordination and analysis of space [21]
Temporal lobe	Auditory perception, comprehension of speech, visual and semantic memory, motivation, the hippocampus and other parts of the limbic system, an evolutionarily earlier part of the cerebrum mostly separate from the cerebral cortex [22,23,27]
Occipital lobe	Primary visual processing [24]

The contralateral relationship of brain to body requires counter-intuitive organization. Visual processing begins in the occipital lobe at the brain's posterior, but optic nerves from the left and right hemispheres cross before reaching the retinal nerves that convert light into electrochemical impulses. The left hemisphere processes the right eye's visual field, and the brain corrects for both its contralateral connections and the fact that retinal images are inverted. Ears rest nearly on top of the parietal lobe's auditory processing regions, but they, too, have primarily links to the opposite hemisphere. The same principle applies to nerves from sensory motor regions which extend to skeletal muscles (voluntary muscles on limbs) via the spinal cord [17]. Thus the right hemisphere controls the left arm and vice versa. Whenever BCI relies on localizing the origin of a physiological signal, system developers must account for the brain's map of the body. This is particularly important because three of the most common interfacing methods – sounds, viewable shapes and imagined movements – are processed contralaterally, that is, on the opposite side of the brain where they are presented, imagined or remembered [18,19].

2.3. Functional organization of the cerebral cortex

Cerebral lobes are associated with a wide range of mental processes. These processes cover some, but by no means all, aspects of human behavior, and considerable research remains to identify the neurophysiological basis of many human activities. Table 1 summarizes the activities typically found in overviews of cerebral lobes.

Functional subdivisions of a cerebral lobe can often be identified with the gyri and sulci that compose it. Table 2 offers a sample of the functional regions often targeted by BCI sensors.

Table 2. A selection of functional regions in the cerebral cortex.

Region	Location	Function
Frontal lobe	Precentral gyrus	Motor control (movement)
Parietal lobe	Postcentral gyrus	Perception of bodily sensations
Temporal lobe	Superior (topmost) temporal gyrus, sulcus between superior and middle temporal gyri	Auditory perception
Occipital lobe	Superior and inferior gyri	Visual perception

Diagrams of cerebral anatomy associate specific structures with function, but, when considering a phrase such as visual cortex or speech center, the word 'primary' is an important qualifier. The brain can be mapped into regions that differ in their cellular organization, and these regions often correspond to meaningful functions. For instance, speech production and comprehension are, respectively, related to Broca's area, which is located in the inferior frontal gyrus [25] and Wernicke's area, which centers on the posterior end of the left temporal gyrus. Attempts to map cerebral regions and to identify regions with functions began in the early 20th century. No consensus on the number of cerebral regions exists, and most researchers admit more work needs to be done, but convincing arguments are made for at least 180 functional regions per hemisphere [14].

Many mental operations do not occur entirely in primary centers, and some studies suggest the borders of a particular region, or even a lobe, are ill-defined or 'more a convenient fiction than anatomical entity' [26,27]. These ambiguities arise from the natural flexibility of brains, anatomical differences among individuals, and the fact that a given operation typically enlists multiple regions. Examples from vision and hearing give a sense of this complexity.

Optic nerves transmit information from retinas to the occipital lobe. After undergoing processing in the occipital lobe, visual signals are then split into two physiologically distinct streams – the dorsal (top) visual stream which runs from the occipital lobe through the parietal lobe, and the ventral (bottom) visual stream which runs from the occipital lobe to the temporal lobe and several subcortical structures [28]. Motor responses, sensory memory and imagination, and conscious awareness enlist even more parts of the brain. While much of the brain's processing occurs in multiple locations or linear streams, its organization does contain identifiable nodes that can interface effectively with BCI. The following example clarifies this statement.

In the early 1960s neuropsychologists discovered a curious phenomenon called right-ear advantage (REA) or left-ear disadvantage (LED). This refers to an experimental user's capacity to discern information presented to the right ear better than the left. These experiments relied on the known position of lesions on the auditory cortex to measure the performance of the right ear/left hemisphere and left ear/right hemisphere in discriminating spoken language. In most of the human population, the left hemisphere controls comprehension of language, but in some people, namely the left-handed, the situation is reversed. As expected, the right ear of right-handed individuals exhibited superior performance (and vice versa), leading researchers to conclude that phonological processing was concentrated in the dominant hemisphere [29]. Later generations of audiologists refined this experimental model, now called dichotic listening, by using EEG to detect how spoken words were perceived, processed and comprehended by the two hemispheres which use the corpus callosum to coordinate auditory data [30]. The results of this experiment will be used to illustrate some of BCI's basic principles later in this paper.

2.4. Structure of the cerebral cortex

Though it is only 2–4 mm thick, the cerebral cortex makes up approximately 80% of the brain's mass. The surface area of each hemisphere is approximately 1,850 cm^2 – 'about the size of a medium pizza' [31] – but, due to convolutions approximately 66% of the brain's surface is folded into sulci [32]. The internal organization of the cerebral cortex is laminar, and it generally has six layers numbered I–VI. However, this number does not hold for all cortical regions, and the quantity, density, thickness and cellular composition of layers varies throughout the cerebral cortex and the cerebral structures located beneath it [13,33].

Each layer of the cerebral cortex consists of tightly packed neurons connected to their neighbors, other layers, and, for some layers, to neurons outside the cerebral cortex. By definition, these latter cells are located under the cerebral cortex. Neurons have a fundamental resemblance to other cells, but, in addition to a central cell body known as the soma, which comes in many shapes, they contain unique features. Most notable are the elongated axons and dendrites. When the axon of one neuron meets the dendrite of another, they form a synapse. Synapses are electrochemical junctions that enable neurons to form complex, relatively high-speed networks, and Figure 5 portrays the distinctive structures of a neuron and a synapse.

The brain also contains a range of cells that support its electrical, biochemical and metabolic functions. Collectively known as glia, these cells support, protect, nourish and insulate neurons, and they are essential for proper cognition as well as health. The primary categories of glial cells are microglia, astrocytes, oligodendrocytes and NG2-glia progenitor cells. Oligodendrocytes are essential to the operation of the brain as an electrical organ because they act as insulators when signals are propagating through axons [34].

Alongside an idealized neuron, Figure 5 depicts an oligodendrocyte cell whose branches enclose the axon of a cerebral neuron in a myelin sheath. While myelin is not essential for neural function, it is used in many classes of neurons within and outside the central nervous system to enhance electrical conduction. In the brain, unmyelinated neurons constitute 'gray matter' while myelinated neurons are called 'white matter' because a mass of fatty myelin has a white appearance [35,36]. Myelin sheaths are punctuated by breaks called Nodes of Ranvier that enable an action potential to propagate efficiently through the length of the axon through a process known as saltatory conduction [37].

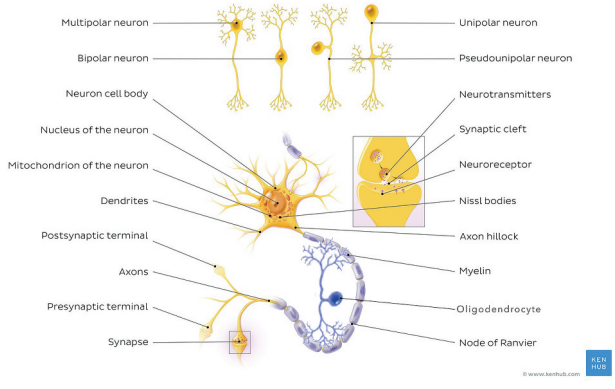

Figure 5. Basic structure of a cerebral neuron [License: Kenhub] .

Neurons do not form simple circuits. Instead axons and dendrites branch, which connects a single neuron to many others. The general term for a neural extension is neurite, and neurites range from a few microns to a meter in length. The complexity of neural networks [31] accounts for the brain's astonishing computational power and the difficulty of describing it in unambiguous terms. A human brain contains approximately 86 billion neurons (20% of which are in the cerebral cortex), and each one participates in multiple processes [38]. Whether in the brain or body, the presence of a myelin sheath offers a way of recognizing neurons. Because cortical neurons are unmyelinated, the outer surface of the brain is gray. Immediately below the gray matter of the cerebral cortex lies white matter, a mass of neurons with myelinated axons that efficiently connect the cerebral cortex with distant regions throughout the brain. We should note that neurons are not the only actively communicating cells in the brain. Glial cells were once considered mere scaffolds, but in recent years researchers have discovered cross-talk between astrocytes and oligodendrocytes [39], and, somewhat surprisingly, oligodendrocytes sometimes form synapses with neurons [34]. Much remains to be discovered about the functional roles of glial cells.

Neurons exhibit many forms, but most layers of the cerebral cortex are dominated by pyramidal neurons, so named for the shape of their soma or cell body. The geometry of pyramidal neurons accounts makes them exceptional candidates for BCI. This is because some layers of the cerebral cortex contain densely packed axons which are perpendicular to the skull's surface [40]. Cortical neurons often fire in synchrony, and the uniform direction of cortical signals (which travel down axons) make them relatively strong – especially if located on a bulging gyrus rather than are ceding sulcus. Figure 6 shows a cross-section of a typical layer of pyramidal cells in the cerebral cortex. An upcoming part of this paper discusses how the layered architecture of the cerebral cortex and its proximity to the skull enables EEG, a sensing technique that is used widely because it is safe, cost effective and sufficiently accurate for many BCI applications.

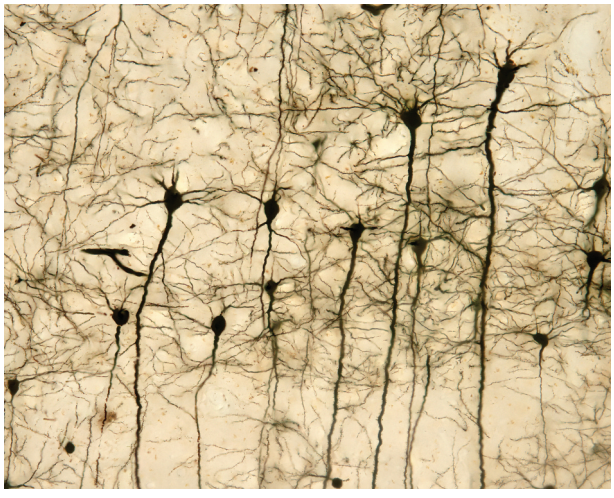

Figure 6. A layer of pyramidal neurons in the cerebral cortex. [License: Shutterstock] .

3. BCI sensors

3.1. Implanted microelectrodes

The use of electrodes to interface with the nervous system began with Luigi Galvani's experiments on frogs in the late 18th century. In the 20th century, it became practical to implant electrodes into living human brains to both record and stimulate mental activity. While the first implants recorded a locality of multiple neurons, for decades it has been possible to insert electrodes called 'patch clamps' into a single neuron using either metal filaments or a glass pipette filled with a conductive fluid [36]. Whether implanted directly into a neuron or recording the activity of a local population, microelectrodes have facilitated enormous progress in neurophysiology and the disciplines which depend on it. Because they can be inserted with precision, implants enable BCI applications to tap the cerebral regions most appropriate to the required output, e.g. control of movement or speech.

But, there are physical limitations on electrode implantation. Conductive materials degrade rapidly in living bodies, and, in turn, they damage organic structures either directly through surgery or through by-products of decay. Practical applications require large numbers of electrodes that are powered, long-lasting, biologically compatible and connected to external transducers. Animal research has been limited by technology and increasing ethical concerns, and, for the same reasons, human studies have been confined to medically justified situations. When allowed, promising results have been obtained as early as 1998, when a single electrode was implanted in the motor cortex of a patient with severe ALS (amyotrophic lateral sclerosis, the 'locked in' syndrome also known as Lou Gehrig's Disease). Although 'locked in', researchers were able to give her control of a computer cursor with a high degree of accuracy shortly before her death [41].

Progress in several related disciplines is making the use of microelectrodes in BCI increasingly feasible. Multiplex, bendable arrays allow a single surgical intervention to perform more tasks. Biocompatible materials

protect tissues and electronics, and microchip-based fabrication processes are bringing new efficiencies and design paradigms to the BCI field. Wireless interfaces reduce disruption of cerebral tissues and infection channels caused by wires through the skull and protective membranes which surround the brain – please see 'A Functional BCI Model by the P2731 working group: Transducer in the same issue for a summary of wireless applications. Later, we will discuss how biomimetic materials are leading advances in implanted electrodes [5,42], but for now medical, technical and ethical issues render the use of microelectrodes in BCI impractical except in research projects.

3.2. EEG

In 1924, the German psychiatrist Hans Berger became the first person to measure the electrical activity of the human brain with an EEG, and his 1929 report introduced the terms alpha waves and beta waves which are still in use [43]. Berger's work built on pioneering studies of animal brains, and he confirmed that human brains produce characteristic waveforms similar to those found in dogs and other animals. By 1947, the American EEG Society was founded [44], and EEG became an important instrument for studying the brain. By the 1970s, UCLA professor Jacques Vidal envisioned the possibility of using EEG to couple brains with computers, and he introduced the term BCI (Brain-Computer Interface) [45].

Berger inserted needle electrodes into the scalp, but, by 1935, noninvasive electrode pads had been introduced [46]. Today EEG is commonly an array of electrode pads placed at regular intervals on the user's scalp. The safe and relatively comfortable noninvasive nature of EEG stands in stark contrast to the invasive surgery required to place microelectrodes into the brain. While both techniques offer temporal resolution of less than 1 millisecond [47], microelectrodes offer superior spatial resolution but are often localized to a certain brain area, while EEG sensor arrays can cover the whole scalp.

EEG arrays range from consumer-grade headbands containing a minimal number of fixed contact points to flexible matrices of 256 sensors that can be placed with precision. Although there are several conventions for naming and placing electrodes, a widely used method is the International 10–20 System portrayed in Figure 7. This approach idealizes the brain as a sphere. Electrodes are placed at increments of either 10% or 20% following standard lines across anatomical extremes. With some exceptions, letters denote the cortical structures below the sensor. For instance, the O-series spans the occipital lobe, and the P-series spans the parietal lobe. Numbers denote an electrode's position on a linear axis [48]. It is important to remember that brains vary in size and shape, so proper placement of electrodes requires training, practice and care.

The majority of EEG sensors gather data about brain activities. However, arrays also include one or more reference electrodes that are used to filter power-line noise and electrical interference generated by muscles and other physiological events. Reference electrodes are often connected to the user's ears but may be placed in other locations.

The example of REA (right-ear advantage) given earlier illustrates how the physiology of the brain both enables and hinders the use of EEG. The phenomenon was reported in 1961, and its conclusions about hemispheric cross-talk were inferred from experimental results. By 2004 researchers could use EEG to measure the effect, not only at each ear but across the brain. Their method was to place a band of sensors between the ears, specifically P7, P3, PZ, P4 and P8 positions shown in Figure 7. The most extreme positions, P7 and P8, are located near the anterior superior temporal gyrus, which contains much of the primary auditory cortex [49].

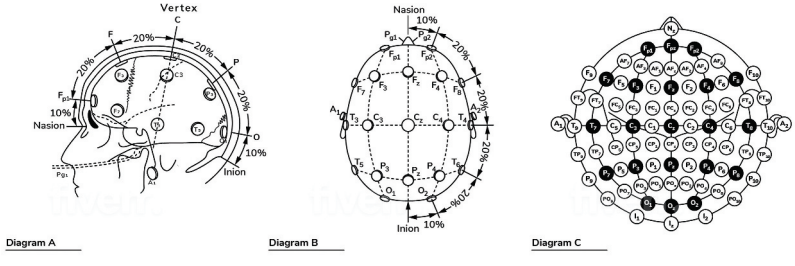

Figure 7. Map of EEG placement points. [Commissioned illustration] .

After presenting stimuli, they searched for the timing of three particular waveforms as they passed between the auditory regions of each hemisphere [30]. These waveforms will be described in a following section.

The study above shows that it is possible to localize electrical phenomena with EEG. However, because the brain and surrounding tissues are both electrically conductive and electrically active, even in resting states, accurate interpretation requires heavy intervention to extract the desired signals from a noisy environment. Extraction techniques are covered in depth by a 'A Functional BCI Model by the P2731 working group: Transducer' in this issue.

3.3. Electrocorticography

Electrocorticography (ECoG) stands between EEG and implanted microelectrodes in safety and accuracy. ECoG requires the skull to be opened, but, unlike the microelectrodes described earlier, sensors are placed on the thick membranes collectively called the meninges that protect the brain – the safest placement point – or directly on the cerebral cortex below the meninges.

As Figure 8 shows, ECoG requires surgery, but it offers advantages over implants and EEG. It is safer than probes which penetrate the brain, and it offers better signal quality than surface probes. ECoG arrays resemble EEG arrays, but, for practical reasons, they cover a smaller area, and thus have more targeted applications that interface with a particular region.

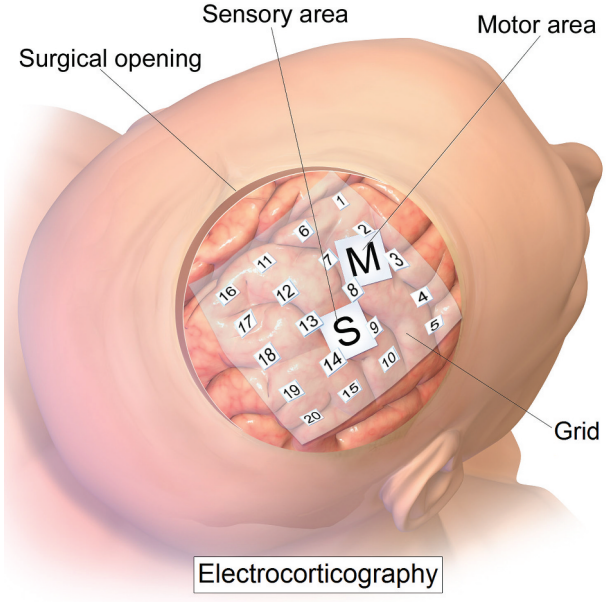

Figure 8. Example of an ECoG implant [License: Creative Commons from 'Medical gallery of Blausen Medical 2014'. WikiJournal of Medicine] .

Though less intrusive than implanted electrodes, ECoG arrays suffer from some of the same issues, notably risk of infection and reduction in sensitivity due to chronic tissue inflammation. These issues are partly determined by where they are placed. The meninges consist of three main layers, the dura (which adheres to the interior surface of the skull), the arachnoid and the pia (which adheres to the outer surface of the brain) [50], and inflammatory responses differ among layers [51]. Wireless systems improve performance while reducing risk of infection. By mapping the folds of an individual's brain prior to implantation, researchers have produced custom-molded ECoG arrays that are more accurate than flat or uniformly curved arrays [51].

3.4. fNIRS

Functional Near-Infrared Spectroscopy (fNIRS) is a head-mounted sensor array. Though its resemblance to EEG is superficial, it is a noninvasive technique that is comparable to EEG in safety and user comfort. Sensor placement can also be determined by existing EEG standards, e.g. the 10–20 system presented above [52].

Where fNIRS diverges from EEG is signal acquisition. Electrodes measure neural signals directly, but the pads used in fNIRS combine light-emitting diodes with optodes which respond to light. Human tissues are effectively transparent to near infrared light. During an fNIRS session, LEDs direct light through the skull at wavelengths between 650 and 850 nm, and receiving optodes measure the scattering and absorption of light once it passes through the brain [53]. fNIRS is a hemodynamic system; namely, it depends on neurovascular coupling. Like any cell, when a neuron becomes active, it demands more oxygen, and neural activity can be tracked by measuring changes in the oxygen levels of cerebral arteries [54]. The term up-regulation refers to the activation of neurons, say the onset of finger tapping in the motor cortex, and neurons signal the need by releasing chemical signals to nearby blood vessels which dilate in response [55]. Unlike electrical impulses which can be recorded in real time, there is a time delay between the onset of a stimulus and the emergence of usable data in an fNIRS system. Oxygenation changes include neural signaling, dilation of nearby capillaries, the delivery of oxygenated blood and the return to metabolic baseline, and the entire process can take up to 10 seconds [56]. Thus, hemodynamic BCI requires longer recording time than its electrical counterparts to obtain similar results.

Although light passes through most biological tissues, the molecules which deliver oxygen to tissues respond differently. Blood cells contain hemoglobin,

a protein that uses iron to bind oxygen, and oxygenated and deoxygenated hemoglobin absorb light at different wavelengths. These conditions enable a typical fNIRS system to record vascular activity in targeted neural regions with spatial resolution of 1–10 mm to a depth of 1.5–2.5 cm below the skull [47,57].

Analyzing the data recorded by fNIRS resembles the workflow, if not analytic methods, required by electrodes. Features must be extracted from background interference, for instance, heart beat, breathing and movements of the head, and then interpreted as mental activity. Though its time resolution is inferior to EEG, fNIRS offers complementary data that is useful in multimodal studies which are increasingly becoming the norm in brain research [47,58].

3.5. fMRI

Similar to fNIRS, functional magnetic image resonance (fMRI) uses hemodynamics to detect mental activity. However, fMRI uses magnetic fields rather than light, an approach that offers advantages and disadvantages relative to other recording techniques.

The primary modality within fMRI is BOLD (Blood Oxygen Level Dependent) MRI. As with light, oxyhemoglobin and deoxyhemoglobin and other components of tissue, respond differently to magnetic fields, and these changes can be tracked by radio pulses. fMRI exploits this trait to pinpoint changes in metabolism that accompany upregulated neural activity. A complementary technique is arterial spin labeling (ASL) MRI which measures cerebral blood flow (CBF). However, ASL's requirements, which include an injected contrast agent, have limited its use [55].

The apparatus used in fMRI differs radically from the BCI methods explained above. Users must lay on their backs, and their head is surrounded, but not touched, by a ring of magnetic sensors. Though safe, the confinement and noise of fMRI can be intimidating to users, and the supine position alters physiological responses to stimuli [59]. Movements by users disturb recording, but efforts to increase the time resolution of fMRI are improving its effectiveness [60].

The main advantages of fMRI over fNIRS and the sensor systems introduced previously is its ability to probe widely and deeply into the brain. Since its invention in 1990, the spatial resolution of fMRI has steadily improved. Conventional systems offer resolution down to 1 mm, and ultra-high resolution systems can inspect the organization of cells in the cerebral cortex [61]. fMRI supports an enormous range of scientific and medical applications. Though it cannot match the convenience of EEG or fNIRS for practical applications in BCI, fMRI is used to discern the neural architecture that directs perception and other mental activities. For instance, fMRI enabled researchers to give functional descriptions of the visual streams mentioned above. By varying the attention of users, it was shown that the dorsal stream processes the position while the ventral stream processes the identity of objects in the visual field [62].

By combining fMRI with techniques which offer superior temporal resolution, neural processes can be accurately localized, sequenced and related to cerebral anatomy. Hybrid systems may combine fMRI with other sensing techniques for simultaneous recording that enhances the design of subsequent BCI applications [63–66].

3.6. MEG

Due to size, cost and complexity, magnetoencephalography (MEG) is more of a diagnostic tool rather than a practical tool for BCI. But MEG is widely used in hospitals, often in conjunction with EEG. In a therapeutic setting, the ensemble is used to diagnose epilepsy and for individual brain mapping prior to surgery. Despite its practical limitations, MEG's method for detecting neural signals is instructive for BCI developers as it reveals yet another approach to sensor design.

Earlier, we remarked that the brain is an electrical organ, and it shares traits with electromechanical systems. As a result of the voltages measured by electrodes, neurons emanate magnetic fields perpendicularly to the direction of their current. As with EEG, MEG benefits from the relatively powerful activity of layered pyramidal cells in the cerebral cortex and other structures within the brain. In contrast to EEG, which detects electrical signals, MEG senses fluctuations in magnetic fields, both on the surface of the experimental user's head. However, in contrast to electrodes, magnetic sensors do not make physical contact with the scalp, nor do they contend with physiological interference.

Biological tissues are almost transparent to magnetic fields, and many fields are canceled by their neighbors leaving a relatively clean signal for interpretation [67]. The downside of MEG is that the brain's magnetic fields are orders of magnitude weaker than the Earth's, so MEG research must be conducted in a magnetically shielded room. Aside from a room with strict environmental requirements, MEG apparatus resembles fMRI from the user perspective. Though they can sit or recline, a dome surrounds the user's head, and MEG sensors inside it must be cooled nearly to absolute zero. Promising new approaches may enhance its relatively poor spatial resolution [68], helping the research community to more accurately map function to structure.

3.7. Categorizing BCI sensors

Figure 9 summarizes the advantages and limitations of commonly used imaging modalities for BCI systems. There are other techniques for brain recording, notably positron emission tomography (PET), but these might be better described as imaging rather than interfacing methods, and they are outside the scope of this paper. Strengths and weaknesses accompany each of the technologies currently in use. None offers the ideal combination of safety, affordability, portability, comfort and high spatiotemporal resolution, which is why BCI methods are increasingly used in tandem as advanced equipment becomes more accessible. For instance, when used simultaneously, fNIRS can be used to improve the spatial resolution of EEG [69].

Several ways of categorizing BCIs are commonly used in scientific literature, notably invasive vs noninvasive and electrical vs. hemodynamic. We have avoided these categories because, while useful in specific contexts, they blur significant issues rooted in physiology. For instance, implanted electrodes, ECoG and scalp-mounted EEG are arguably the same electrical technology, but they differ in invasiveness, accuracy and ease of use. EEG and fNIRS contrast in signal acquisition, but they are similar in safety, ease of use and cost. fMRI, MEG and techniques such as PET require large installations which erect high barriers to use.

Rapid advances in materials science and sensing technologies may also blur categories. Tandem recordings taken by different systems have been used to improve the design of safer, more convenient systems [70]. And entirely new approaches have produced unprecedented improvements in foundational technologies. For example, the introduction of optical techniques have shrunk experimental MEG sensors to the size of chips that work at room temperature. It is conceivable that a radically evolved MEG will one day approach EEG in cost and convenience [68,71].

Advances in analysis are equally important. Analytics are supported by improvements in generic models of the brain which allow meaningful results to be extrapolated from relatively poor data sets [72], and the P2731 work group is advocating standardization of data formats and experimental documentation that can accelerate the consolidation of experimental results. In this situation, without ignoring useful categorizations, we think it is best to keep an open mind as to which technologies will define the future.

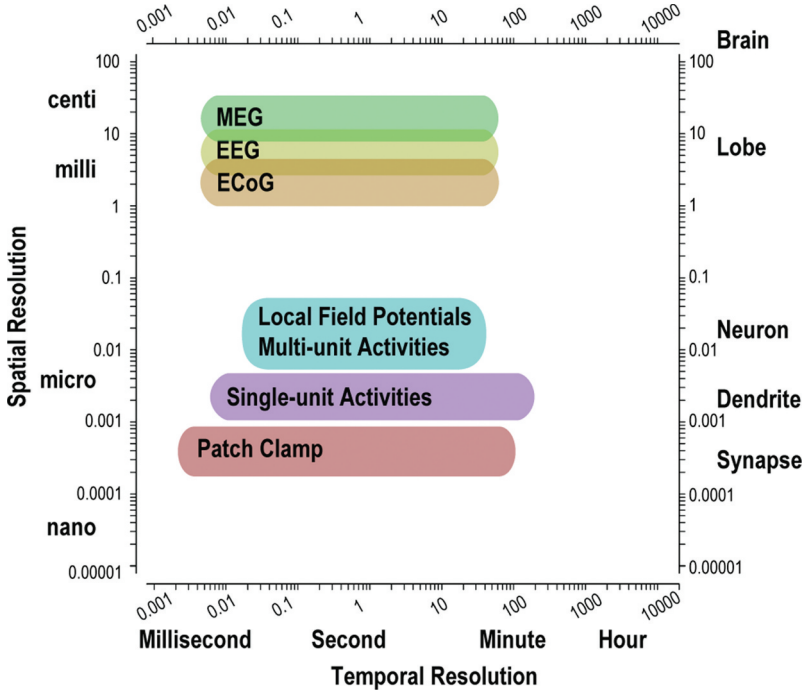

Figure 9. Various brain signal acquisition methods and their spatiotemporal extent [206] .

4. Typical signals used in BCI

Since the discovery of alpha waves in the 1920s, researchers have identified numerous forms of electrical signals in the brain. For BCI to deliver its promise – mental control of external devices – a neurophysiological signal must be consistent, detectable and clearly express an intention. While progress continues, some signals have already become de facto standards in BCI. This section will review the signals most commonly used in BCI along with their physiological context [73]. For more information about the origin, propagation and detection of the brain's extracellular electrical signals, see Buzsáki and others [74].

4.1. Action potentials

Like all cells, a membrane separates the interior of neurons from their surroundings which are typically other cells and extracellular fluids. Neuronal membranes are selectively permeable to ions, and they use ion pumps to actively maintain a voltage difference of −40 mV to −90 mV with their surroundings. This difference is known as the neuron's resting potential. Resting potential resists perturbations up to a certain threshold, but, when a stimulus is strong enough to cross the threshold, a neuron rapidly changes polarity by reversing its ionic balance as shown in Figure 10. In a matter of milliseconds, the neuron's interior becomes as much as 50 mV positive relative to its external medium, and, during the course of its response, it may change polarity several times before returning to its resting state. This radical depolarization causes the neuron to 'fire', that is, to transmit signals to connected neurons. After depolarization, a neuron typically passes through a refractory period where no level of stimulus will change its polarity. A depolarization event is known as the action potential or firing of a neuron, and its propagation to connected neurons via axons form the fundamental signals of mental activity [75].

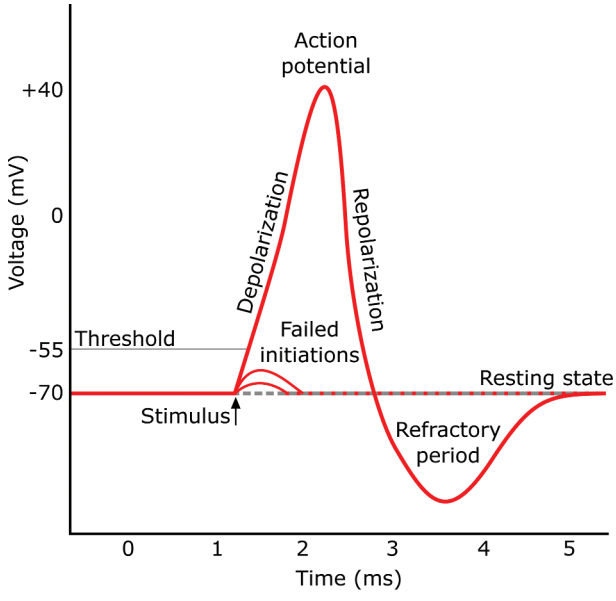

Figure 10. Typical waveform generated by an activated neuron [License: Chris73, Wikimedia Commons] .

Recording action potentials requires highly localized sensors such as patch clamps or microelectrodes which have been placed with great precision. Another approach uses plasticity, the brain's capacity to alter its structure, to improve results. Earlier we described an experiment where a microelectrode was implanted into the motor cortex of a patient with advanced ALS. The microelectrode was coated with neurotrophic factors that encouraged neurites in the area of interest to grow into the hollow tip of an electrode. Within weeks, the recording apparatus began detecting action potentials, and on Day 45 the researchers began training the patient to control a cursor [41].

In the future, neurons could be integrated with BCI via neurotrophic electrodes – essentially synthetic nerves – that insinuate themselves into the natural brain by forming synapses that both sense and modulate action potentials. For now direct measurement of action potentials is limited to experiments on animals and justified medical interventions. Although use of action potentials is currently unfeasible, the concept is important for understanding BCI because neurons work in concert: millions of neurons working together produce signals that reach the scalp. But, like the brain, pathways to measurement are also convoluted. In the case of EEG, research has shown that an action potential occurs too rapidly to create significant activity on the scalp. Instead EEG measures the longer lasting consequences of neural firing, the so-called postsynaptic potentials of cortical pyramidal cells. These temporarily change the cell into an electrical dipole, that is, a body that is negatively charged at one end and positively charged at the other [73]. As the next section shows, much of what BCI measures is not the direct electrical activity of neurons, whether one or millions, but the cascade of physiological effects that follow on the firing of neurons.

4.2. Local field potentials

Populations of neurons can be targeted with extracellular electrodes implanted in the region of interest. In these cases, electrodes are recording local field potentials (LFPs). It is generally accepted that an LFP represents a variety of voltage fluctuations generated by target

populations of neurons [76]. Despite years of study, questions of how LFPs are generated, their spatial extent, and how they relate to signals acquired by different sensing methods, e.g. fMRI vs. EEG, are ongoing subjects of investigation [77–79]. The varying structures of neurons demonstrate and often cause the challenges associated with signal acquisition.

So far, we have mainly discussed pyramidal neurons in the cerebral cortex. Like trees, these neurons have a well-defined apex and trunk-like structure that enables them to function like dipoles. The same characteristics that make pyramidal layers of the cerebral cortex accessible to EEG may activate LFP sensors. But, if this were the case, then spherical neurons in non-laminar structures – such as the medium-sized spiny neurons in the striatum, a cluster beneath the cerebral cortex – would cancel each other out because their electrical fields would randomly interfere with each other. This is not the case, so more complex hypotheses are being investigated [80].

Primate and human studies with implanted LFP sensors have shown promising results in the control of robotic prostheses. In some cases, LFPs outperform systems which record action potentials [81,82]. For instance, primates with implants that measure LFPs in the parietal reach region (PRR), a section of the parietal cortex connected to the motor cortex, have shown that experimental subjects can quickly learn to perform direction of movement tasks. These results would likely transfer to humans, and LFP sensors have the advantage of degrading more slowly than single-cell implants [82]. Though safer than patch clamps, for now the dangers associated with implants limit the use of LFP sensors within humans. Data gathered by invasive mapping of LFPs in other species have supported the development of noninvasive tools for humans, but this progress has occurred mostly through analytics rather than material advances [83]. As long-term implants to detect LFPs become feasible, understanding 'the geometry of the[se] neural currents' can be used to optimize the design of electrodes for controlling prostheses and other applications [84].

4.3. Event-related potentials

Event-related potentials (ERP) are voltage fluctuations generated when regions of the brain respond to stimuli, prepare for a movement or perform mental operations such as imagining movement. When sensed by EEG, ERPs are detected as consistent changes in microvoltage levels on the scalp, but these changes are usually masked by higher amplitude background noise. To compensate, 'time locked signal averaging is necessary to extract ERPs from the raw data' [85]. This method requires researchers to segment a recording into a series of 'epochs' that begin with the stimulus that causes the ERP [86]. ERPs are time-locked to stimuli, so an epoch should be long enough to include the stimulus, a precursor period of background data, and sufficient time to capture the ERP under scrutiny. Averaging a set of epochs allows the time-locked signal to emerge by decreasing the relative amplitude of noise [87]. ERPs have been identified for different sense modalities, but localizing their neural generators has proven difficult because of the head's conductive properties [88,89]. ERP names are created by combining their polarity – P for positive, N for negative – with their peak latency, namely the time between a stimulus and their maximum amplitude measured in milliseconds (e.g. N250, P300) or the order in which they appear (e.g. P1, N2, P2). Note that both the onset and the maximum amplitude of an ERP are in reality variable, and it is the stereotypical waveform combined with temporal proximity to an hypothetical post-stimulus peak that enables researchers to categorize it [90–93].

The discovery of REA (right-ear advantage) given above illustrates the use of ERPs. Recall that the experiment was conducted by measuring electrical activity across the band of scalp connecting the ears of experimental users. A great deal of electrical activity is available at every sensor, so researchers used analytic techniques to extract the ERP as it peaked at each sensor. The ERP in question has three components: the N1, the P2 and the P300 which is also known as the late positive component. For simplicity, we can define the N1-P2 as a waveform complex that characteristically occurs about 200 ms after a stimulus. It may be thought of as the brain's acknowledgment of an auditory event. As the next section describes, the P300 is a relatively strong waveform that recognizes unique or 'oddball' events, and it typically peaks 300 ms after the stimulus. In the context of REA experiments, the P300 signals recognition of a word. The researchers verified this assumption, and the hypothesis that phonological processing occurs in the dominant hemisphere, by comparing when ERPs arrived at each recording site. The N1-P2 acknowledgment – 'a sound has been heard' – appeared simultaneously in the auditory cortex of both hemispheres, but the P300 – 'a sound has been interpreted' – appeared first in the dominant auditory cortex then propagated to the opposing hemisphere [30]. Essentially, the dominant auditory cortex interpreted the meaning of the sound before sharing it with its counterpart. The process happens too quickly to notice in natural hearing.

EEG has high temporal resolution, so it is a good choice for capturing the amplitude, a measure of signal strength, of events that occur in less than a second. Earlier we noted that fNIRS can be used to improve the spatial resolution of EEG interpretations. This can also be done

with fMRI, and now we see why progress in neurophysiology, e.g. understanding the spatial location of neural tracts, supports improvements in BCI design [94]. Recent publications offer indices of sensory, motor, and cognitive functions associated with ERP paradigms [92], and the P2371 working group's goal is to provide models for combining these data. With sufficient work on signal localization, it may be possible to design external prostheses that operate more naturally by interfacing more accurately with the brain's processing centers for hearing, vision, speech, touch and movement.

4.4. P300 evoked potential

The P300 evoked potential is one of the most common waveforms used in BCI systems. We have seen that P300s respond to specific forms of auditory stimuli, and the same applies to visual and somatosensory stimuli. Despite its name, a P300 can take as long as 900 ms to reach maximum amplitude [95].

The visual P300 has two significant components which seem to differ in spatial and temporal distribution [96,97], but the details are both unresolved and beyond this paper's scope. What is important for BCI design is its measurable parameters: amplitude and latency. Amplitude refers to the strength of the signal, and latency is the time between stimulus and the P300's detection. Both can be used to interpret the degree of mental activities such as surprise and recognition, and also to describe the mental processes required to compare perceptions with memories.

Because it can be extracted with relative ease, the P300 signal is used in many control systems including the P300 Speller detailed in other papers within this special issue. It can also serve as a diagnostic tool because it provides evidence of possible disorders in attention, learning and other traits without reports from the user [49].

4.5. Neural oscillations

We mentioned that Hans Berger described alpha and beta waves, also called neural oscillations, in his 1929 report on EEG. Thus, neural oscillations have been studied during the entire history of BCI, and, in the popular imagination, they are one of the primary physiological correlates with mental activity. Neural oscillations are created by large numbers of neurons firing in synchrony. Associations with the broadly drawn psychological states charted below are still valid, but neural oscillations are now recognized as signals that coordinate activities across the brain. Section 5 will introduce some of these new horizons.

Standard accounts classify neural oscillation in the following ranges. As is often the case with brain studies, the boundaries of each category overlap in different references, and many researchers divide canonical bands into sub-bands that are distinguished either by frequency or location [98].

Delta (.5–4 Hz): Slow waves with relatively high amplitude generated during non-REM (rapid eye movement) sleep [99].

Theta (4–8 Hz): Waves associated with various aspects of cognition and behavior, including drowsiness, learning, memory, and spatial navigation [99].

Alpha (8–13 Hz): Waves representing wakeful relaxation, usually recorded from the visual cortex, and spontaneously beginning when a user closes their eyes [100].

Mu (8–12 Hz): Oscillations in the same range as alpha are known as mu-rhythms when recorded over sensorimotor areas [101].

Beta (13–30 Hz): Associated with waking consciousness, they represent active mental concentration [102].

Gamma (30+ Hz): Waves associated with higher level cognitive functions such as memory, attention and perception [103].

It may be tempting to directly relate neural oscillations with the localized signals detailed earlier. In simple but fallacious equations, action potentials aggregate to local field potentials which in turn aggregate to event-related potentials, when generated singularly, and neural oscillations in the brain's holistic state. However, this is not the case. Each of these phenomena are generated by different causes, and, in addition to physiological ambiguities which are still being investigated, the categories we use to measure neural activity may reflect technical or conceptual constructs.

Putting aside ambiguities, neural oscillations are important physiological tools for BCI. They are relatively easy to isolate, and it is simple to present them as feedback to BCI users. By attending to feedback, many BCI users can learn to willfully produce a particular oscillation. Since oscillations are associated with relaxation, attentiveness and other useful states, feedback systems can support psychological well-being and self-control. Along with the P300, detection of neural oscillations can provide insights into the effectiveness of messaging, e.g. for marketing or vocational training. And, because they can be recorded by rudimentary EEG arrays, neural oscillations can also provide an interface signal for games, machine operation and other forms of digital engagement.

4.6. Sensorimotor rhythms & motor imagery

Sensorimotor rhythms are produced by the primary motor (M1) and sensory areas (S1). These areas are depicted in the precentral and postcentral gyri in Figures 2 and 4, and in EEG they are prominent in the sensors adjacent to electrode CZ in Figure 7 [104], especially C3 and C4 [105] Taken together, these regions form the sensorimotor cortex (SM1) surrounding the central sulcus that separates the frontal and parietal lobes. These well-mapped areas are adjacent to the skull, and thus they are a prime target for EEG and MEG, both of which are more sensitive to signals, specifically changes in amplitude, that emanate from the surface of the cerebral cortex [106].

Sensorimotor rhythms (SMR) oscillate in the μ band of 8–12 Hz often with beta (~20 Hz) and gamma (~40 Hz) components [107]. SMRs are a resting or 'idling' oscillation [108]; that is, they manifest most strongly when an individual is awake but at rest.

SMRs are important for BCI because bodily motion is largely under conscious control. This means users can modulate the amplitude of SMRs by initiating or imagining movements, for instance, grasping a glass of water [109]. SMRs are convenient for users because they can be generated by responding to easily understood suggestions. SMRs are particularly useful for BCI because imagined movement produces responses similar to actual movement.

Motor imagery (MI) is defined as 'mental rehearsal of a motor act without any movement execution' [110]. Even when paralyzed, most people can imagine moving a specific limb to the left, right, up or down, and the act of imagination generates activity in the corresponding region of the motor cortex. Note that this activity is contralateral to the part involved. Figure 11 shows how regions of the sensorimotor cortex map to a homunculus that corresponds to relevant areas of the body [111]. The motor cortex controls movement decisions, memories and imagination, and changes in SMRs are the physiological correlates of these mental activities [1,112].

Detection of MI depends on event-related desynchronization (ERD). Prior to action, whether physical or imagined, the motor cortex attenuates the idling μ-rhythm in a process called desynchronization. Desynchronization weakens the amplitude of μ-rhythm components, and it signals that an individual has engaged the sensorimotor system by deciding to move or imagining movement. When the activity ends, and the sensorimotor cortex returns to its resting state, the μ-rhythm reappears in event-related synchronization (ERS). Regular detection of

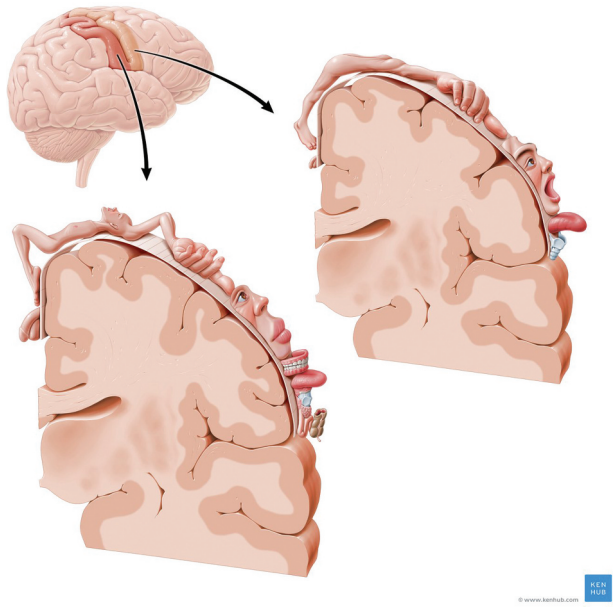

Figure 11. A visualization of the homunculus in a cross-sections of the motor and sensory cortex [License: Kenhub] .

ERD/ERS enables a BCI (sometimes called an SMR-BCI) to interpret commands. During a series of training sessions, users practice imaginary movements with hands, fingers and feet. Feedback is given, often through a cursor on a computer screen, to enable the user to consciously generate distinctive neuronal patterns. These patterns can then be used to control a computer, an exploratory robot or interactive games which enhance quality of life for locked-in users [108].

SMR-BCI can also be used for rehabilitation of organic functions. Typically, the BCI operator asks the user to imagine moving a hand or foot. For instance, they could focus on tapping their fingers or mentally practice more complex motions such as playing tennis [113,114]. One study has shown that active feedback in the form of a mind-controlled cursor accelerates rehabilitation of stroke victims. Though it utilizes an external prosthesis, this form of therapy relies on neural plasticity, in this case, the brain's capacity to re-route signals around damaged areas. Not all BCIs aim to replace nerves; in these BCI-based therapies, the combination of BCIs with assistive technologies stimulates organic regeneration [115].

4.7. Steady state visual evoked potentials

Steady state visual evoked potentials (SSVEP) are a class of visual evoked potentials (VEP). VEPs are modulations that originate in the occipital lobe, and, similar to

other evoked potentials, they exhibit characteristic waveforms named for polarity and latency. Because the amplitude of VEPs increases when users focus on a stimulus, they are relatively easy to induce and detect. VEPs can be classified as either transient (TVEP) or steady state (SSVEP) by their frequency. TVEPs are less than 6 Hz, while SSVEPs are greater than 6 Hz, and, as their name implies, occur continuously. SSVEPs are popular for BCI because they produce strong, localizable signals that peak at the frequency of the stimulus, and they are easy to induce from a variety of light sources [77,116].

SSVEPs result when neurons collectively entrain themselves to oscillating stimuli. This is usually presented as a set of lights or a checkerboard that flickers by alternating its black and white squares [49]. By focusing on particular elements of the presentation, users can direct an EEG to perform an action. The occipital lobe responds quickly and consistently to visual phenomena, and SSVEP systems can be designed to work with little training on the part of the user or BCI transducer [1,117].

Another use of SSVEPs, albeit one which lies outside the range of BCI is medical diagnosis. In this configuration, the sensors are used as a mental probe rather than a control interface. Flashing or patterned lights produce a characteristic P100 latency in the occipital lobe. Also known as the P1, this waveform appears 100 ms after the stimulus in healthy individuals. Deformation in the timing or amplitude of the P100 response indicates inflammation or other abnormalities in visual pathways [77].

4.8. Categorizing BCI signals

Numerous typologies of neural activity are found in BCI literature. Two categories are relevant to the P2731 Functional Model: exogenous and endogenous [118]. Exogenous signals are physiological responses to stimuli. For instance, a researcher may incorporate a flashing light, image or sound into their system. Endogenous signals are produced in the course of the brain's routine operation, e.g. self-regulation, or by conscious efforts on the part of the user, e.g. when a user imagines tapping their fingers [77,118]. Though not used here, the categories of exogenous and endogenous physiology are incorporated into the P2731 Glossary and Functional Model because we think they will be useful for categorizing unified data sets in the future. What remains is to categorize multimodal signals. To achieve complicated interactions, future BCI applications will require either signals from different regions of the brain or multimodal feature extraction from existing sensory arrays. New analytic techniques have begun enabling the latter approach [119], and they could enable users to control more than one parameter of an actuator simultaneously [82]. Examples of applications include inflecting speech with emotion or controlling the force of grip when handling objects with a prosthetic limb.

5. Emerging BCI paradigms

Traditionally, the brain has been treated as a low-frequency electrical instrument with a characteristic range of 1–60 Hz. However, further studies have revealed this is due to technical limitations of EEG. In fact, the skull and surrounding tissue acts as a low-pass filter that effectively eliminates high-frequency waves. Growing bodies of evidence point to meaningful activity between 0.01 and 500 Hz. At the same time, coupled BCI instrumentation and new forms of analysis, many driven by machine learning, are discovering new purposes for the canonical frequency bands [64], and with these new purposes have come a host of new concepts for describing the operation of the brain: cross-frequency coupling, co-modulation, temporal framing and precession [120].

This section introduces a selection of outlying frequency bands and interpretations of cerebral signaling which may grow in importance as new sensors and analytic tools emerge. If so, they may impact BCI design by enabling brain–machine interactions that are safer, more effective and more natural from the user perspective.

5.1. Slow cortical potentials

Slow cortical potentials (SCP) are low-frequency shifts in EEG ranging from 0.01 to 0.1 Hz that are distinct from well-known delta waves [121]. SCPs precede or accompany imagined movement or cognitive tasks, and, in keeping with their function, they are concentrated over the frontal motor regions [116,122]. Research points to a strong correlation between SCPs and a user's behavior including attention, preparation and motivation [123]. Though SCPs are mainly produced in the cerebral cortex, they respond to connections with the thalamic attention system [122]. The thalamus is a cluster of neurons beneath the cerebral cortex that functions as a hub for sensory and motor signals, and it is thus closely tied to decisions and motivations.

SCPs are endogenous signals that control attention and, in a broader sense, inhibit impulses. Because they are amenable to individual self-control with BCI-assisted neurofeedback, they offer hope for both

therapeutic and applied BCI. Studies have shown that learning to generate SCPs via neurofeedback (SCP-NF) mitigates epilepsy in many patients who are otherwise resistant to treatment. Because SCPs regulate attention [122], SCP-NF could possibly assist individuals with ADHD. Some studies show promise, but others have been inconclusive. One intriguing study has shown that experienced meditators are able to control SCPs more effectively than untrained users, but the benefits of this ability have yet to be defined medically [121]. It could be that SCP-NF is effective only when combined with other therapeutic or environmental interventions [124,125].

SCPs have been used as an alternative to P300 evoked potentials for spelling systems, and some researchers believe they could be used as thought translation devices that control sounds, lights and wheelchairs [126]. As purely endogenous phenomena, SCPs have greater potential than other signals for paralyzed or 'locked in' users who may not be able to focus on exogenous stimuli such as visual images.

5.2. High frequency oscillations (HFOs)

Not long ago, all neural oscillations that exceeded 30 Hz were lumped together under the classification gamma. Exploration of high-speed oscillations were limited by technology, and research focused on them as biomarkers of epilepsy. However, epilepsy is one of the few conditions that permits the ethical insertion of electrodes into the human brain, and, in tandem with animal studies, studies of epileptic patients showed that healthy brains produce ultra-high oscillations, sometimes called fast gamma, that range from 110 to 160 Hz [127], ripple oscillations that range from 100 to 250 Hz [128], and other oscillations, as yet unnamed, that may reach 500 Hz.

While ethics and technology limits research into HFOs, it is now acknowledged that there are one or more frequency bands above gamma. To date they have been most frequently recorded in the occipital cortex, the hand motor area [129] and the hippocampus, an inner region of the temporal cortex that is crucial to memory. Since they often occur during periods of sleep associated with memory consolidation, some researchers associate HFOs with the formation of memory, a process which involves replaying incidents during non-REM sleep [130,131]. Normative values for HFOs have yet to be established, but researchers are working to establish common naming conventions, frequency ranges and functional descriptions [129,132]. These oscillations may one day have application in some of the advanced forms of BCI described below.

5.3. Cross-frequency coupling

One of the brain's most tantalizing qualities is the quantity of processing it performs within a compact, low-power structure. Many of the brain's components serve multiple purposes, and an exciting area of research reveals how physiological structures may work in tandem through cross-frequency coupling (CFC). Section 4.5 summarizes six frequency bands – delta through gamma – that have been identified with operational states of the brain. A growing body of research demonstrates that these canonical frequency bands do not operate in isolation. Instead, they interact in a structured manner to coordinate activities in different regions in the brain. For example, one study showed that the phase of theta oscillations modulates the power of fast gamma oscillations [133]. By enabling signals to perform multiple duties, CFC may contribute the brain's astonishing efficiency

An hypothesis of growing interest is that cross-frequency coupling enables local and global processes to interact and thus supports the integration of distributed information [134]. Memory and learning would be examples of this integration which requires the retention of stimuli from a perceptual center to working memory [135]. Various forms of cross-frequency coupling have been identified by experiments, including phase/amplitude, phase/phase, amplitude/amplitude, phase/frequency and phase/amplitude coupling [136]. This may explain both the architectural complexity and tremendous efficiency of the brain. Interactions among different neural clusters may occur so signals can cross-modulate to carry multiple messages, reinforcement or even forms of analysis. Within this framework, slower oscillations may provide temporal frames for faster ones, and the precession of one oscillation relative to another may carry information in its own right.

Phase-amplitude coupling (PAC) is the most common example of CFC. PAC 'reflects the coupling of the phase of oscillations in specific frequency bands to the amplitude of oscillations in another frequency band' [137]. Numerous studies have found correlations between theta and gamma oscillations [136,138,139]. Studies of humans, non-human primates and other mammals have found that the amplitude of gamma oscillations is phase-locked to theta oscillations while performing memory tasks. Efforts to correlate EEG and hemodynamic signals outside well-recognized frequency bands revealed that the phases of infraslow fluctuations of less than 1 Hz (SCPs) synchronize with amplitudes of faster activity. Although the evidence is

not conclusive, this might represent one of the mechanisms the brain uses to coordinate overall or network-wide activities [140].

It is necessary to explain how the distributed topology of the brain integrates activities across specialized regions [136], and cross-frequency coupling is an elegant solution to the problem. In 2005 some researchers hypothesized that future EEG experiments will reveal an oscillatory hierarchy in the brain. They describe this as a 'systematic dependence of higher frequency oscillatory amplitude on lower frequency phase' [141]. Much research to date has found evidence of CFC, but it is worth bearing in mind precautionary arguments. Analytic techniques revealing new forms of CFC have improved [142], but there is still no accepted explanation of the physiological mechanisms underlying the phenomena, and CFC remains a rich field of scientific investigation [143]. As the causes of CFC emerge, they would become integral to BCI design because they would enable more accurate multimodal control of actuators, for instance, allowing users to inflect synthesized speech with emotional emphasis with less effort than current systems.

5.4. Bidirectional BCI

Electrodes have shrunk steadily since Galvani's experiments, and the microelectrodes of today can be used to induce action potentials in a single neuron. Depending on the location, direct electrical stimulation, also called modulation, results in sensations which feel more or less natural to users. Within BCI electrical stimulation can provide feedback to users that enhance performance. For instance, it can offer a sense of resistance that improves a user's ability to grasp objects with a robotic arm. BCI that incorporates neural modulation is known as bidirectional BCI [144].

Before discussing direct stimulation of the central nervous system we should note that the brain is not the only region of the body that can be electrically modulated. Direct electrical stimulation can induce sensations in peripheral nerves, and, by the same token, neural impulses can be detected in peripheral nerves located under the skin and within skeletal muscles. Electromyography (EMG) sensors are readily available for noninvasive detection of neuromuscular activity, and they have been used in the muscles of amputees and intact individuals to control external actuators such as prosthetic arms. Microelectrodes implanted in the same area can generate sensations in the phantom limb that has been replaced with a prosthesis [145] Moving closer to the brain, cochlear implants have substantially restored hearing [146], and retinal implants have imperfectly restored vision [147–149]. Restoring vision presents paradigmatic challenges in neuroprosthetic design because it requires biocompatible materials and high-density arrays to replace retinal fields [150,151]. For some applications, interfacing with the peripheral nervous system is safer, more convenient and less expensive than BCI.

There are situations where cerebral implants are the only viable option for interfacing with users. Neuromuscular interfaces still rely on the brain for intentional control, and the central nervous system of individuals with neurodegenerative diseases or spinal cord injury may lack access to peripheral nerves. Because of its complexity, the brain also offers more options for control than peripheral nerves [152], though reaction times lag behind natural somatosensory control [153].

Electrical modulation of the brain is accomplished through intracortical microstimulation (ICMS), a process which involves sending a low-amplitude electrical pulse through an implanted microelectrode. Minimum thresholds range from 1 to 17 μA, but currents up to 500 μA are used in experimental situations. An ideal system would target single neurons, but the electrical fields generated by ICMS influence populations of neurons near the target as well as passing axons. Thus the 'one neuron' precision attainable by recording has not been matched by stimulation technologies, and this may account for the 'partially natural' quality users ascribe to artificial sensations [154].

Successful bidirectional BCI mainly involves the somatosensory cortex. While any neuron in the brain can be artificially stimulated, users are oblivious to stimulation in many regions, and the perceptual responses of specialized regions such as the occipital lobe, which produces visual patches called phosphenes [147], may not be helpful for applications that require tactile feedback. In contrast, the somatosensory homunculus illustrated in Figure 11 enables researchers to generate sensations of pressure in distinct surfaces of the body including fingers. By intensifying the amplitude of a signal to a maximum of 100 μA, researchers generated a sensation of increasing pressure in users, a capacity which would prove useful in manipulating objects in the real world [155].

An example of this application is lifting an egg or another delicate object with a prosthetic arm. Positioning the arm can be achieved visually, but grasping without damage requires proprioception and tactile sensitivity to pressure. Users have traditionally used visual feedback to achieve such tasks, and some systems

have augmented natural vision with intelligent systems that compensate for the lack of proprioception and tactile capacity. Examples include an AR (Augmented Reality) display [156] and control modules that automatically calibrate the movement of prostheses to user intentions [157]. Only recently has ICMS advanced to the point where it can be used as part of the user feedback loop, and the results from single user studies are promising. In one study, microstimulation of the somatosensory cortex, graduated from 20 μA to 90 μA to simulate applied force, improved grasp force accuracy when the user gripped a virtual object [158]. In another study, a user achieved unprecedented performance as scored by the Action Research Arm Test (ARAT). This study involved a tetraplegic user moving a variety of objects with a robotic arm while the areas of his somatosensory cortex corresponding to palm and fingers received ICMS [159].

Challenges remain for bidirectional BCI based on ICMS. Microelectrodes produce gross effects relative to the subtle dance of excitation, inhibition and oscillation that characterizes natural signaling [160]. Perceptions are assembled from different processing streams, which makes it difficult to induce coherent phenomena. For instance, there is not a one-to-one correspondence between visual phenomena and visual processing areas. In an additional wrinkle, the relationship between saccades (the natural scanning movements of the eyes) and the neural map of the retina in the occipital cortex seemingly shifts the position of phosphenes generated by ICMS [147]. Generating a biomimetic sensation requires an apparatus that coordinates multiple inputs into multiple regions of the brain to operate within shifting arrays of cycles, processes and processing hierarchies.

To maintain phenomenological stability, such an apparatus may also need to adapt to changes in the brain's neural environment. After it undergoes stimuli, the brain reconfigures itself by setting new thresholds and synaptic associations. Under more radical conditions, such as lesions, brains may compensate by pressing new channels into service. The brain's capacity to reconfigure itself, known as neural plasticity, presents obstacles to long-term implants, and, aside from the possibility of damage discussed elsewhere, further research into the brain's adaptive response to artificial stimulation is needed. An alternative to biomimetic stimulation is arbitrary stimulation which leads to new forms of learned behavior. Humans and other primates have learned to operate BCI applications by responding to artificial stimuli that have no correlation to natural phenomena. If the psychological impact is not negative, future users of BCI may simply adopt new sensory modalities [161].

To close, it should be noted that BCI can serve to rehabilitate as well as replace organic neural functions. In patients with brain damage, feedback from BCI systems encourages their brains to form new neural pathways to replace damaged ones [162–164]. In these cases, BCI is a temporary therapeutic tool that encourages regrowth of organic capacity.

5.5. Biohybrid systems

Neural plasticity describes the adaptive capacity of the brain. It is expressed physiologically in the brain's capacity to revise its neurological order, and it is expressed psychologically in growing levels of skill and comfort that occur in adept BCI users. Physiological and psychological plasticity underlies the potential of permanent implants to enable a full range of BCI controlled applications [165].

Decades of experimentation demonstrate the capacity of engineered systems to integrate with the natural faculties of humans and other animals. During BCI training sessions for operating prosthetic limbs and other actuators, individuals usually start with motor imagery such as flexing a hand without actually doing so. Studies using motor imagery have shown that many individuals eventually skip images in favor of direct feedback from the actuator, e.g. the cursor on a computer screen [166]. The same principle applies to non-human primates and even rats who start with movement before learning that movement is unnecessary to control external actuators [167]. One user of a prosthetic limb reported "that she was thinking about the goal of the action, such as 'grab the block', rather than issuing kinematic commands . . . suggesting that the control was intuitive" [168]. In essence, the prosthesis becomes an appendage controlled by intention rather than protocols. Studies with EEG have shown that a single cortical area starts performing multiple functions after BCI training [82]. This plasticity may be an avenue to the multimodal control necessary for complex tasks, but it is too early to generalize about the most effective design of BCI recording arrays. Whole brain studies that combine EEG with fMRI indicate that even simple tasks enlist dispersed processing centers that localized research may miss [169]. The sense of agency which makes BCI intuitive may depend on interaction with more regions than a successful experiment reports.

Materials science constitutes a primary vehicle for safe permanent implants that would enable mainstream use of BCI. Other sections of this paper discuss the physiological limitations of materials currently used in long term (or chronic) brain implants. Advances in noninvasive technologies such as EEG and transcranial magnetic stimulation (TMS) [170] may avoid problems involved with implantation, but, because surface sensors provide noisier signals, medical difficulties are offset to the transducer module where signals are interpreted.

Noninvasive sensor arrays may also present the issue of wearability. If head or body gear is required, cerebral implants may be more practical for long-term applications.

As discussed earlier, ethical considerations have limited experimentation with implants. However, these considerations are being mitigated by the use of in vitro preparations of live neurons grown on an extracellular matrix and sustained by a fluid culture that provides oxygen, nutrients, antibiotics and growth factors. Experiments prove that these cerebral organoids self-organize into networks which behave similarly to cerebral tissues in an organism [165]. Therapeutic interventions continue to improve and supply a growing basis of evidence for the efficacy of BCI. A recent study with a single ALS patient demonstrated that an ECoG array remained stable for 3 years. The user's satisfaction with the device increased during the test period – 'without [it] I would be without words' – and the subdural implant caused no medical issues [171]. It is clear that permanent implants could circumvent limitations imposed by a variety of neurophysiological illnesses, and they would also support valuable industrial, military and commercial applications [3]. While considerable room for improvement remains, signal processing modules and control interfaces already have the capacity for high-stakes applications in medicine. Improvements in artificial intelligence (AI) and computer hardware will reduce the cost of accurately interpreting neural activity, and they will do the same for the actuators and modulators required for intuitive user control. What remains is the development of biohybrid systems that enable long-term or permanent use of implanted BCI hardware.

Biohybrid systems arise from the combination of BCI with biocompatible materials and techniques for integrating them with the nervous system. We have already discussed neurotrophic factors that induce nerves to grow into electrodes. These early experiments were limited by the use of materials which either corrode or cause scarring that renders them useless because the brain is an adverse environment for traditional electronics [172]. Implants which resist corrosion face other issues. When the brain senses a foreign object, glial cells form a thick layer to isolate it from neurons. This immune response may result from surgical damage, but it also arises from the brain's rejection of implant materials. Silicon, carbon and tungsten evoke glial cell formation and neural depletion that interfere with probe interfaces [173]. Initially, it was thought that coatings may stabilize implants [174] while flexible probes with polymer substrates would cause less damage and better conform to the brain's convolutions [175,176]. Ever smaller probes approach the nanometer scale of the smallest neural structures. But these innovations mitigate rather than eliminate damage caused by implants [9,177]. A growing body of work concludes that current generations of invasive probes suffer from a 'fundamental structural, mechanical and topological difference' between implants and cerebral tissues. As measured by Young's modulus, a way of measuring the tensile strength of a material, the brain is extraordinarily soft: even flexible probes are still 100,000 to 1,000,000 times more rigid than cerebral tissue [178]. Anything more rigid than the brain exerts shearing pressure that damages cerebral tissue and provokes an immune response.

Mechanics alone do not describe the profound mismatch with the materials commonly used in implants. Cerebral tissues resemble a hydrogel in their ability to diffuse solutes such as ions, oxygen and nutrients, and implants need to match this capacity, or they will disrupt the finely tuned three-dimensional functioning of the brain [177]. Entirely new technical paradigms are required to achieve biocompatibility. One area of progress is mesh electronics.

Mesh electronics operate on the premise that nonliving neural probes must 'look and behave' like neural tissue [179]. A neural mesh overlays a porous 3D substrate with nanowire field-effect transistor (FET) detectors that are smaller than cells. The resulting array overcomes many of the deficiencies of previous generations of neural probes. They can be rolled into a cylinder and implanted through a syringe in a minimally destructive procedure. After departing the syringe, they unfurl to accurately target individual cells. Mesh architecture gives the array the behavior of a colloid in solution, and after implantation neurites grow through the porous netted array which also allows diffusion of nutrients and other solutes. Sensors and modulators (stimulating electrodes) can be incorporated into a single array, and the scale of functional probes enables the formation of artificial synapses that enable integration with natural tissue [178].

So far, we have discussed the use of BCI as a replacement for the peripheral nervous system, that is, as an interface between the brain and external actuators. Biohybrid systems could also enable the implantation of cerebral prostheses. Researchers have proposed that a combination of neural recording and stimulating arrays could bypass damaged areas of the brain. For instance, if a section of the visual stream in the parietal cortex is damaged, a BCI bypass could enable visual information to be conducted from the occipital cortex to the frontal cortex to enable planning for movement [180]. Technological intervention is not limited to perceptual and motor functions.

Experiments combining theta-burst transcranial magnetic stimulation (TBS) of the hippocampus with fMRI have shown it is possible to enhance memory [65], and the convergence of biological neural networks (BNN) with artificial neural networks (ANN), could enable more ambitious systems for 'injecting information' into the cerebral cortex [165]. In principle, BCI applications could provide cognitive as well as sensory and physical prostheses.

Progress in biohybrid systems which combine cultured neural tissue with artificial neural networks is advancing toward a form of interfacing which enables organic tissues to integrate permanently with tissue-like bidirectional implants. With progress in safety, cost and functionality, biohybrid BCI systems could become the basis for new and widely available categories of therapeutic interventions. And, if society allows, they may extend human capabilities well beyond our natural endowment.

6. Physiological impediments to signal acquisition

Numerous conditions impede the detection of signals in the brain. Impediments can be divided into two categories: intrinsic, that is, originating in the human user, and extrinsic, that is, artifacts that originate in the BCI apparatus or its environment [181]. While some impediments have particular characteristics, BCI researchers face a primary problem: in the brain, signals of interest are often far weaker than competing inputs. This section will review the physiological sources of electrical signals that interfere with study of the brain.

6.1. Electromyographic activity (EMG)

Action potentials are not limited to neurons. Muscle cells generate action potentials to contract, and, when multitudes act synchronously, their aggregate contraction produces bodily movement. Muscles in the face and neck are relatively powerful compared to cerebral neurons. They are often physically closer to brain sensors, and, without the insulation of the skull and the brain's protective membranes, they easily interfere with detection of cortical potentials [182].

6.2. Electrooculographic activity (EOG)

Structural features of the eye, namely ionic differences between its components, create a powerful dipole near EEG sensors [183]. Movements of the eye are a major source of noise in EEG because electrical fields produced by ocular movement resemble the frequency of cerebral waveforms but have greater amplitude [181]. In EEG, a primary use of reference electrodes is to filter interference from EMG and EOG.

6.3. Skin potential artifacts (applies to EEG)

Electrodermal activity, movement and perspiration can create skin potentials that resemble SCPs [183]. Before placing electrodes, skin should be carefully cleaned to provide the lowest possible impedance between the sensor and the subdermal signals used to control BCI applications [184]. EEG sensors can be either wet or dry. As the name implies, dry electrodes are placed on a user's scalp without a coating. They are more convenient to set up and more comfortable for users, but they have lower conductivity than wet electrodes. Coating electrodes with a saline solution or conductive gel has been considered critical to achieving accurate results, but it requires discomforting skin abrasion, skilled technicians and periodic renewals of the conductive substance. A recent study has concluded that contemporary dry electrodes can achieve comparable results to wet electrodes [185], and some organic dry electrodes outperform traditional sensors in accuracy, durability and user comfort. It is likely that progress in skin probe fabrication will continue, and the need for invasive probes could lower with each phase of improvement [186]

6.4. Signal composition (applies to EEG)

Because tissue acts as a low-pass filter, scalp-mounted electrodes are most sensitive to neuronal activity in a relatively low range of frequencies. This corresponds to the well-documented oscillations occurring between 1 Hz and 90 Hz [6].

6.5. Surgical damage

Invasive techniques involve opening the skull and implanting electrodes at depths that start at the brain's surface and proceed deeper. Insertion of sensors risks hemorrhage and damaging neurons and the tissues which support and nourish them. There are well-established techniques for avoiding and mitigating the immediate effects of surgical wounds [187,188]. However, microscopic damage to the blood–brain barrier (BBB) often persists, and the resulting accumulation of neurotoxins reduces the efficacy of electrodes while posing risks to the user [7].

6.6. Biological tissue responses

As with other tissues, the brain responds to medical implants through inflammation and other defensive processes called the foreign body response (FBR). The chronic damage to the BBB described above is an example of a FBR, and other FBRs isolate, corrode or reduce the sensitivity of electrodes while simultaneously damaging cerebral tissues. Our understanding of how the brain responds to chronic implants is far from complete, and the reaction of cerebral tissues to foreign substances is an obstacle to delivering the promise of BCI. Problems range from structural changes, e.g. the formation of protective layers such as glial scar tissue around electrodes [172], to chemical interactions with bodily fluids which release neurotoxins [189,190].

6.7. Heat generation

Cerebral tissue starts to burn at 38°C [51], so the generation and dissipation of heat is an important consideration in the design of implantable BCI systems.

6.8. Movement

The effects of movement vary widely among BCI platforms. EEG and fNIRS allow some movement on the part of users. Implants are limited only by the sturdiness of their external connections and the inevitable exposure of the brain. Facial movements present special problems to EEG because electrical signals produced by muscles are far stronger than mental activity. Movement during fMRI and MEG degrades the quality of data which must be precisely registered, or assigned to the same position in the brain, to extract meaningful measurements from epochs.

6.9. Fatigue & aging

In this paper, we are treating the brain as a component of an engineered system – the P2731 Functional Model – and engineering requires consistency. Consistent states are difficult to achieve because brains differ among individuals. However, individual performance also differs between sessions and even within a single session [191]. Like muscles, brains fatigue, and long sessions or challenging tasks may cause a user's performance to decline [192,193]. To develop mainstream applications, researchers need to allow distractions that simulate real-world conditions [194]. As discussed above, rapid mental fatigue is especially common in individuals with ALS. The plasticity of the brain also affects performance over a longer term: connections among neurons acclimate with practice, or as discussed in Section 5.4, they may reorganize in response to electrical stimuli.

Aging presents different challenges. Structures such as the dura mater, the protective layer surrounding the brain, thickens with age. This increases the force required to insert electrodes through it [195], and it raises the question whether its electrical properties change. Finally, mental performance declines with age. While behavioral observations correlate to speed, at the neurological level, the phenomena of aging are related to more complex causes than a decline in the linear rate of stimulus response [196,197].

Differences among and even within individuals impact other elements of the BCI system, notably the classifier module which is trained to recognize signals. As discussed in the following section, even methods with large and well-established datasets such as the P300 speller require individual calibration, a condition which hampers the deployment of BCI applications outside of laboratories.

6.10. BCI illiteracy

Individual variation affects both the acquisition of data and active efforts by users to control actuators via BCI. As we have emphasized, the brains of normally functioning people are not identical, and, in the absence of scans or surgery, the position of anatomical features can only be estimated by researchers. Attention, imagination and other mental activities that produce detectable responses are products of skill, strength and endurance [198]. As with athletics, some individuals excel at BCI applications while a sizable population are unable to produce acceptable results. The latter condition is often called 'BCI illiteracy' [66,109]. Unfortunately, some of the populations who may benefit the most from BCI, e.g. individuals with ALS, may have impairments which hinder them from engaging with the technology. There are efforts to predict BCI performance on the basis of relevant physiological indicators, e.g. the resting state of SMRs, and, if validated by further experiments, they may improve training regimens or, at the least, help avoid costly and uncomfortable failures [193]

6.11. P300 latency jitter

In engineering, jitter is uncontrolled variability in the time window of a signal's arrival. Because the P300 is the foundation of many BCI control systems, individuals who exhibit jitter, that is, variations in the timing of P300 responses, may be unable to take advantage of

neuroprostheses. Latency jitter occurs in neurotypical individuals, and it has been associated with a broad range of conditions that includes schizophrenia, trauma to the brain and aging [196,199]. Unfortunately, evidence points to a class of individuals who stand to benefit most from P300 spellers and other actuators: people diagnosed with ALS or who are in a vegetative or minimally conscious state. Research continues into the causes of P300 latency jitter and the classes of people at risk, and further insight may inform the design of future systems [199,200]. A promising method is latency estimation. Researchers augmented the signal interpretation stage with an additional layer of classification, and, although problems remained, they were able to improve the results of individuals with marginal BCI performance [191,201].

7. Conclusions

Repeatability is the bedrock of science, and BCI-based research has been fortunate in this regard. From inception EEG revealed phenomena, namely the alpha to gamma neural oscillations, which are universal in healthy brains. Furthermore, analogous neural oscillations occur across species. Experiments on primates and other mammals reveal a continuum of evolutionary development, and they guide insights into the neurophysiology of humans [202,203]. Although the behavioral correlates of early discoveries are now recognized as simplifications, they provided a solid foundation for scientific advance along with the confidence that investments in research would produce progress [204].

Advances in methods and key technologies are accelerating progress in BCI. Studies that combine platforms, e.g. EEG and fMRI, are revealing how signals propagate through the brain, and, by creating more accurate models, they offer ways to improve the design of compact systems [109]. The combination of biocompatible materials, nano-components, AI-driven analysis and biohybrid technologies are overcoming physiological impediments to implementation of BCI in non-medical settings. While still on the horizon, these factors are bringing long-term or even permanent electrophysiological implants closer to reality, and strong arguments for the superiority of permanent implants have been made [5,6]. At the same time, improvements in noninvasive techniques may obviate the need for surgery in some scenarios. Some researchers are already considering the security, privacy and governance issues raised by an 'Internet of Neurons' that may emerge from ubiquitous BCI [205].

Another barrier to the progress of BCI is the absence of shared terminology and data formats. This paper covers the terms that inform the physiology module of the IEEE P2731 working group's functional model, and it will be reflected in the standard glossary the group plans to release in late 2021. Improvements in BCI, notably the spatiotemporal resolution of data, ensures that BCI-based science will be a dynamic field, and it would not be surprising if new paradigms of mental operation emerge in the near future. Given the pace of progress in BCI, it is vital to reach consensus on how to document data and, indeed, how to discuss it across disciplines.

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Disclosure statement

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References

[1] McFarland DJ, Wolpaw JR. EEG-based brain-computer interfaces. Curr Opin Biomed Eng. 2017;4:194–200.
[2] Quaresima V, Ferrari M. Functional near-infrared spectroscopy (fNIRS) for assessing cerebral cortex function during human behavior in natural/social situations: a concise review. Organizational Res Methods. 2019;22(1):58.
[3] Beveridge R, Wilson S, Coyle D. 3D graphics, virtual reality, and motion-onset visual evoked potentials in neurogaming. Prog Brain Res. 2016;228:329–353.
[4] U.S. FDA guidance for offers a compendium of the hazards associated with brain implants: implanted Brain-Computer Interface (BCI) devices for patients with paralysis or amputation - non-clinical testing and clinical considerations, May 20, 2021
[5] Woeppel K, Yang Q, Cui, XT. Recent advances in neural electrode–tissue interfaces. Curr Opin Biomed Eng. 2017;4:21–31.

[6] Stephan W. Invasive vs. non-invasive neuronal signals for brain-machine interfaces: will one prevail? Front Neurosci. 2016;10. 10.3389/fnins.2016.00295http.
[7] Saxena T, Karumbaiah L, Gaupp EA, et al. The impact of chronic blood-brain barrier breach on intracortical electrode function. Biomaterials. 2013 Jul;34 (20):4703–4713.
[8] Hong G, Lieber CM. Novel electrode technologies for neural recordings. Nat Rev Neurosci. 2019;20(6):330–345.
[9] Fei H, Lycke R, Ganji M, et al. Ultraflexible neural electrodes for long-lasting intracortical recording. iScience. 2020;23:8.
[10] Rihani RT, Stiller AM, Usoro JO, et al. Deployable, liquid crystal elastomer-based intracortical probes. Acta Biomater. 2020;111:54–64.
[11] Kliemann D, Ralph Adolphs J, Tyszka M, et al. Intrinsic functional connectivity of the brain in adults with a single cerebral hemisphere. Cell Rep. 2019;29(8):2398–2407.e4.
[12] Carne RP, Vogrin S, Litewka L, et al. Cerebral cortex: an MRI-based study of volume and variance with age and sex. J Clin Neurosci. 2006;13(1):60–72.
[13] Zilles K, Palomero-Gallagher N. Cyto-, myelo-, and receptor architectonics of the human parietal cortex. NeuroImage. 2001;14(1):S12.
[14] Glasser MF, Coalson TS, Robinson EC, et al. A multi-modal parcellation of human cerebral cortex. Nature. 2016 Aug 11;536(7615):171–178.
[15] Van Essen DC, Drury HA, Joshi S, et al. Functional and structural mapping of human cerebral cortex: solutions are in the surfaces. Proc Nat Acad Sci. 1998;95(3):788–795.
[16] Gogolla N. The insular cortex. Curr Biol. 2017;27(12): R580–R586.
[17] Halpern ME, Güntürkün O, Hopkins WD, et al. Lateralization of the vertebrate brain: taking the side of model systems. J Neurosci. 2005 Nov 9;25 (45):10351–10357.
[18] Paradigms MI, Rupawala M, Dehghani H, et al. Shining a light on awareness: a review of functional near-infrared spectroscopy for prolonged disorders of consciousness. Front Neurol. 2018;Article 350:5.
[19] Gratton G. The contralateral organization of visual memory: a theoretical concept and a research tool. Psychophysiology. 1998;35(6):638–647.
[20] Sira CS, Mateer CA. Frontal Lobes. In: Aminoff MJ, Daroff RB, editors. Encyclopedia of the neurological sciences. Second ed. Boston, Massachusetts, USA: Academic Press; 2014. p. 358–365.
[21] Goldberg ME. Parietal lobe. international encyclopedia of the social & behavioral sciences. 2001. London, UK: Elsevier; p. 11051–11054.
[22] Simons JS, Johnsrude IS. Temporal lobes. In: Aminoff MJ, Daroff RB, editors. Encyclopedia of the neurological sciences. Second ed. Boston, Massachusetts, USA: Academic Press; 2014. p. 401–408.
[23] Rogalsky C. Chapter 47 - the role of the anterior temporal lobe in sentence processing. In: Hickok G, Small SL, editors. Neurobiology of language. Boston, Massachusetts, USA: Academic Press; 2016. p. 587–595.
[24] Deyoe EA, Lobe O. Encyclopedia of the human brain. Boston, Massachusetts, USA: Academic Press; 2002. p. 677–715.
[25] Foundas AL, Knaus TA, Shields J. Broca's area. In: Aminoff MJ, Daroff RB, editors. Encyclopedia of the neurological sciences. Vol. 544. Second ed. Boston, Massachusetts, USA: Academic Press; 2014.
[26] Karbe H. Note that the borders of Wernicke's area vary in different studies, Wernicke's area. In: Aminoff MJ, Daroff RB, editors. Encyclopedia of the neurological sciences. 2nd ed. Boston, Massachusetts, USA: Academic Press; 2014. p. 751–752.
[27] Tanaka K. Temporal Lobe. In: Smelser NJ, Baltes PB, editors. International encyclopedia of the social & behavioral sciences. Oxford, UK: Pergamon; 2001. p. 15595–15599.
[28] Sheth Bhavin R, Ryan Y. Two visual pathways in primates based on sampling of space: exploitation and exploration of visual information. Front Integr Neurosci. 2016;10; pp. 1–2.
[29] Kimura D. Cerebral dominance and the perception of verbal stimuli. Cana J Psychol. 1961;15(3):166–171.
[30] Jerger J, Martin J. Hemispheric asymmetry of the right ear advantage in dichotic listening. Hear Res. 2004;198 (1–2):125–136.
[31] Van Essen DC, Donahue CJ, Glasser MF. Development and evolution of cerebral and cerebellar cortex. Brain Behav Evol. 2018;91(3):158–169.
[32] My-MS. The cerebrum. [cited 2021 Jul 02]. https://my-ms.org/anatomy_brain_part1.htm
[33] Zilles K, Palomero-Gallagher N, Amunts K. Cytoarchitecture and maps of the human cerebral cortex. In: Toga AW, editor. Brain mapping. Boston, Massachusetts, USA: Academic Press; 2015. p. 115–135.
[34] Sarah J, Leda D. Glial cells and their function in the adult brain: a journey through the history of their ablation. Front Cell Neurosci. 2017;11:8.
[35] Wen HT, Rhoton AL, Mussi ACM. Surgical anatomy of the brain, chap 2. In: editor, Winn HR. Youmans and winn neurological surgery. 7th ed. Philadelphia, PA: Elsevier; 2017. p. 173;
[36] Levitan IB, Kacmarek LK. The neuron. Oxford, UK: Oxford University Press; 2015. p. 33.
[37] Britannica. The Editors of Encyclopaedia. "Node of Ranvier". Encyclopedia Britannica. 2021. 2018 Dec 5, https://www.britannica.com/science/node-of-Ranvier .
[38] Levitan IB, Kacmarek LK. The neuron. Oxford, UK: Oxford University Press; 2015. p. 8–14.
[39] Nutma E, Van Gent D, Amor S, et al. Astrocyte and oligodendrocyte cross-talk in the central nervous system. Cells. 2020;9(3):600.
[40] DeFelipe J, Fariñas I. The pyramidal neuron of the cerebral cortex: morphological and chemical characteristics of the synaptic inputs. Prog Neurobiol. 1992;39 (6):566–567.
[41] Kennedy PR, Bakay RA. Restoration of neural output from a paralyzed patient by a direct brain connection. Neuroreport. 1998 Jun 1;9(8):1707–1711.
[42] Bartels J, Andreasen D, Ehirim P, et al. Neurotrophic electrode: method of assembly and implantation into human motor speech cortex. J Neurosci Methods. 2008;174(2):168–176.

[43] Tudor M, Tudor L, Tudor KI. Hans Berger (1873-1941): povijest elektroencefalografije [Hans Berger (1873-1941): the history of electroencephalography]. Acta Med Croatica. 2005;59(4):307–313.
[44] Britton JW, Frey LC, Hopp JL, et al., authors Louis EK, Frey LC, editors. Electroencephalography (EEG): an introductory text and atlas of normal and abnormal findings in adults, children, and infants [Internet]. Chicago: American Epilepsy Society; 2016. Appendix 6. A Brief History of EEG.
[45] Vidal J. Toward Direct Brain-Computer Communication. In: Mullins LJ, editor. Annual review of biophysics and bioengineering. Vol. 2. Palo Alto: Annual Reviews, Inc.; 1973. p. 157–180.
[46] Gibbs FA, Davis H, Lennox WG. The electro-encephanlogram in epilepsy and in conditions of impaired consciousness. Arch NeurPsych. 1935;34 (6):1133–1148.
[47] Quaresima V, Ferrari M. Functional near-infrared spectroscopy (fNIRS) for assessing cerebral cortex function during human behavior in natural/social situations: a concise review. Organizational Res Methods. 2019;22(1):46–68.
[48] . American electroencephalographic society guidelines for standard electrode position nomenclature. American Electroencephalographic Society; J Clin Neurophysiol. 1991;8(2):200–202. Journals@Ovid Full Text. Web. 28 November. 2020.
[49] Linden DEJ. The P300: where in the brain is it produced and what does it tell us? Neuroscientist. 2005;11(6):569.
[50] Haines DE. Neuroanatomy: an atlas of structures, sections, and systems. 4th ed. Philadelphia, Pennsylvania, USA: Williams & Wilkins; 1995. p. 46.
[51] Matsushita K, Hirata M, Suzuki T, et al. A fully implantable wireless ECoG 128-channel recording device for human brain–machine interfaces: w-HERBS. Front Neurosci. 2018;12:511.
[52] Paola P, Felix S, Antonia H, et al. Current status and issues regarding pre-processing of fNIRS neuroimaging data: an investigation of diverse signal filtering methods within a general linear model framework. Front Hum Neurosci. 2019;12:6.
[53] Rupawala M, Dehghani H, Lucas S, et al. Shining a light on awareness: a review of functional near-infrared spectroscopy for prolonged disorders of consciousness. Front Neurol. 2018;Article 350:2.
[54] Buxton RB, Frank LR. A model for the coupling between cerebral blood flow and oxygen metabolism during neural stimulation. J Cereb Blood Flow Metab. 1997 Jan;17(1):64–72.
[55] Glover GH. Overview of functional magnetic resonance imaging. Neurosurg Clin N Am. 2011 Apr;22(2):133–9, vii.
[56] Buxton RB, Wong EC, Frank LR. Dynamics of blood flow and oxygenation changes during brain activation: the balloon model. Magn Reson Med. 1998;39 (6):855–864.
[57] Rupawala M, Dehghani H, Lucas S, et al. Shining a light on awareness: a review of functional near-infrared spectroscopy for prolonged disorders of consciousness. Front Neurol. 2018;9(350):2–3.
[58] Curtin A, Ayaz H. Chapter 22 - Neural efficiency metrics in neuroergonomics: theory and applications. In: Ayaz H, Dehais F, editors. Neuroergonomics. Boston, Massachusetts, USA: Academic Press; 2019. p. 133–140.
[59] Quaresima V, Ferrari M. Functional near-infrared spectroscopy (fNIRS) for assessing cerebral cortex function during human behavior in natural/social situations: a concise review. Organizational Res Methods. 2019;22(1):47.
[60] Stehling MK, Turner R, Mansfield P. Echo-planar imaging: magnetic resonance imaging in a fraction of a second, For instance, echo-planar imaging (EPI). Science. 1991 Oct 4;254(5028):43–50.
[61] Larkum Matthew E, Petro Lucy S, Sachdev Robert NS, et al. A perspective on cortical layering and layer-spanning neuronal elements. Front Neuroanat. 2018;12:4–6.
[62] Kropotov JD. Chapter 3.1 - Sensory systems and attention modulation. In: Kropotov JD, editor. Functional neuromarkers for psychiatry. Academic Press; Boston, Massachusetts, USA; 2016. p. 140–142. DOI:10.1016/B978-0-12-410513-3.00011-5.
[63] Gopikrishna D, Rangaprakash D, Luke O, et al. A new generation of brain-computer interfaces driven by discovery of latent EEG-fMRI linkages using tensor decomposition. Front Neurosci. 2017;11. DOI:10.3389/fnins.2017.00246.
[64] Michel Christoph M, Denis B. EEG source imaging: a practical review of the analysis steps. Front Neurol. 2019;10. DOI:10.3389/fneur.2019.00325.
[65] Hermiller MS, Chen YF, Parrish TB, et al. Evidence for immediate enhancement of hippocampal memory encoding by network-targeted theta-burst stimulation during concurrent fMRI. The Journal of Neuroscience. 2020;40(37):7155–7168.
[66] Zich C, Debener S, Kranczioch C, et al. Real-time EEG feedback during simultaneous EEG–fMRI identifies the cortical signature of motor imagery. NeuroImage. 2015;114:438–447.
[67] Singh SP. Magnetoencephalography: basic principles. Ann Indian Acad Neurol. 2014;17 (Suppl 5):S107–12.
[68] Zhang R, Xiao W, Ding Y, et al. Recording brain activities in unshielded Earth's field with optically pumped atomic magnetometers. Sci Adv. 2020;6 (24):eaba8792.
[69] Rupawala M, Dehghani H, Lucas S, et al. Shining a light on awareness: a review of functional near-infrared spectroscopy for prolonged disorders of consciousness. Front Neurol. 2018;Article 350:7.
[70] Waldert S, Preissl H, Demandt E, et al. Hand movement direction decoded from MEG and EEG. J Neurosci. 2008;28(4):1000–1008.
[71] Sander TH, Preusser J, Mhaskar R, et al. Magnetoencephalography with a chip-scale atomic magnetometer. Biomed Opt Express. 2012;3 (5):981–990.
[72] See PROFESSOR Petra Ritter's virtual brain project: [cited 2021 Jun 25]. https://www.thevirtualbrain.org/tvb/zwei

[73] Kirschstein T, Köhling R. What is the source of the EEG? Clin EEG Neurosci. 2009;40(3):146–149.
[74] Buzsáki G, Anastassiou C, Koch C. The origin of extracellular fields and currents — EEG, ECoG, LFP and spikes. Nat Rev Neurosci. 2012;13(6):407–420.
[75] Levitan IB, Kacmarek LK. The neuron. Oxford University Press; Oxford, UK, 2015. p. 34–36.
[76] Harilal P, Bipin N, Egidio D, et al. Computational modeling of single neuron extracellular electric potentials and network local field potentials using LFPsim. Frontiers in Computational Neuroscience. Vol 10, p. 1, 2016] [Pesaran B. Uncovering the mysterious origins of local field potentials. Neuron. 2009;61(1):1–2.
[77] Nicolas-Alonso LF, Gomez-Gil J. Brain computer interfaces, a review. Sensors. 2012;12(2):1221–1223.
[78] Logothetis NK, Pauls J, Augath M, et al. Neurophysiological investigation of the basis of the fMRI signal. Nature. 2001;412(6843):150–157.
[79] Harilal P, Bipin N, Egidio D, et al. computational modeling of single neuron extracellular electric potentials and network local field potentials using LFPsim. Front Comput Neurosci. 2016;10:65.
[80] Tanaka T, Nakamura KC, Charpier S. Focal inputs are a potential origin of local field potential (LFP) in the brain regions without laminar structure. PLoS One. 2019;14(12):e0226028.
[81] Mehring C, Rickert J, Vaadia E, et al. Inference of hand movements from local field potentials in monkey motor cortex. Nat Neurosci. 2003;6(12):1253–1254.
[82] Andersen RA, Musallam S, Pesaran B. Selecting the signals for a brain-machine interface. Curr Opin Neurobiol. 2004 Dec;14(6):720–726.
[83] Waldert S, Preissl H, Demandt E, et al. Ad aertsen, carsten mehring. hand movement direction decoded from MEG and EEG. J Neurosci. 2008;28 (4):1000–1008.
[84] Pesaran B. Uncovering the mysterious origins of local field potentials. Neuron. 2009 Jan 15;61(1):1–2.
[85] Brandeis D, Lehmann D. Event-related potentials of the brain and cognitive process: approaches and applications. Neuropsychologia. 1986;24(1):153.
[86] Kropotov JD. Chapter 1.6. In: Kropotov JD, editor: Functional neuromarkers for psychiatry. Academic Press; Boston, Massachusetts, USA; 2016. p. 59.
[87] De Pascalis V. On the psychobiology of extraversion, In R. M. Stelmack (Ed.), On the psychobiology of personality: Essays in honor of Marvin Zuckerman; pp. 295–298; Elsevier Science. https://doi.org/10.1016/B978-008044209-9/50017-8. 2004.
[88] Woodman GF. A brief introduction to the use of event-related potentials in studies of perception and attention. Atten Percept Psychophys. 2010;72 (8):2031–2046.
[89] Creel DJ Visually evoked potentials. Webvision, 29 Nov 2020
[90] Comerchero MD, Polich J. P3a and P3b from typical auditory and visual stimuli. Clin Neurophysiol. 1999;110(1):24–30.
[91] Polich J. Updating P300: an integrative theory of P3a and P3b. Clin Neurophysiol. 2007;118(10):2130.
[92] Kappenman ES, Farrens JL, Wendy Zhang W, et al. ERP CORE: an open resource for human event-related potential research. NeuroImage. 2021;225:117465.
[93] Kropotov JD. Chapter 3.1 - Sensory systems and attention modulation. In: Kropotov JD, editor. Functional neuromarkers for psychiatry. Boston, Massachusetts, USA: Academic Press;; 2016. p. 66. DOI:10.1016/B978-0-12-410513-3.00011-5.
[94] Marchesotti S, Martuzzi R, Schurger A, et al. Cortical and subcortical mechanisms of brain-machine
[95] Linden DEJ. The P300: where in the brain is it produced and what does it tell us? Neuroscientist. 2005;11 (6):563–576.
[96] Polich J. Updating P300: an integrative Theory of P3a and P3b. Clin Neurophysiol. 2007;118(10):2128–2148.
[97] Morgan KK, Luu P, Tucker DM. Changes in P3b latency and amplitude reflect expertise acquisition in a football visuomotor learning task. PLoS One. 2016;11 (4):2: e0154021.
[98] Kropotov JD. Chapters 1-6, 2-2, 2-3l. In: Functional neuromarkers for psychiatry. Cambridge, Massachusetts, USA: Academic Press; 2016. p. 6–7.
[99] Abhang PA, Gawali BW, Mehrotra SC. Chapter 2 - Technological basics of EEG recording and operation of apparatus. In: Abhang PA, Gawali BW, Mehrotra SC, editors. Introduction to EEG- and speech-based emotion recognition. Cambridge, Massachusetts, USA: Academic Press; 2016. p. 19.
[100] Kropotov JD. Chapter 3.1 - Sensory Systems and Attention Modulation, Editor(s): Juri D. Kropotov, Functional Neuromarkers for Psychiatry, Academic Press, Cambridge, Massachusetts, USA, 2016.
[101] Kropotov JD. Chapter 2.2 – alpha rhythms. In: Levy N, editor. Functional neuromarkers for psychiatry. San Diego: Academic Press; 2016. p. 89–105.
[102] Kropotov JD. Chapter 3 - Beta rhythms. In: Kropotov JD, editor. Quantitative EEG, event-related potentials and neurotherapy. Cambridge, Massachusetts, USA: Academic Press; 2009. p. 59.
[103] Başar E, Başar-Eroğlu C, Özerdem A, et al. Preface: application of brain oscillations to neuropsychiatric diseases: a new land? In: Başar E, Başar-Eroğlu C, Özerdem A, et al., editors. Supplements to clinical neurophysiology. Vol. 62. Amsterdam, The Netherlands: Elsevier; 2013.
[104] Gomez-Rodriguez M, Peters J, Hill N, et al. Closing the sensorimotor loop: haptic feedback facilitates decoding of motor imagery. J Neural Eng. 2011;8(3):036005.
[105] Cheng MY, Hung CL, Huang CJ, et al. Expert-novice differences in SMR activity during dart throwing. Biol Psychol. 2015 Sep;110:212–218.
[106] McFarland DJ, Krusienski DJ, Wolpaw JR. Brain-computer interface signal processing at the Wadsworth Center: mu and sensorimotor beta rhythms. Prog Brain Res. 2006;159:411–419.
[107] Engel AK, Fries P. Chapter 3 - Neuronal oscillations, coherence, and consciousness. In: Laureys S, Gosseries O, Tononi G, editors. The neurology of consciousness. Second ed. Cambridge, Massachusetts, USA: Academic Press; 2016. p. 51.

[108] Kübler A, Mattia D. Chapter 14 - Brain–computer interface based solutions for end-users with severe communication disorders. In: Laureys S, Gosseries O, Tononi G, editors. The neurology of consciousness. Second ed. Boston, Massachusetts, USA: Academic Press; 2016. p. 217–240.
[109] Botrel L, Kübler A. Week-long visuomotor coordination and relaxation trainings do not increase sensorimotor rhythms (SMR) based brain-computer interface performance. Behav Brain Res. 2019 Oct 17;372: 111993.
[110] Alkadhi H, Brugger P, Boendermaker SH, et al. What disconnection tells about motor imagery: evidence from paraplegic patients. Cereb Cortex. 2005 Feb;15 (2):131–140.
[111] Boulay CB, Sarnacki WA, Wolpaw JR, et al. Trained modulation of sensorimotor rhythms can affect reaction time. Clin Neurophysiol. 2011 Sep;122(9):1822.
[112] Zapała D, Zabielska-Mendyk E, Augustynowicz P, et al. The effects of handedness on sensorimotor rhythm desynchronization and motor-imagery BCI control. Sci Rep. 2020;10(1):2087.
[113] Krusienski DJ, Schalk G, McFarland DJ, et al. A mu-rhythm matched filter for continuous control of a brain-computer interface. IEEE Trans Biomed Eng. 2007 Feb;54(2):273–280.
[114] Rupawala M, Dehghani H, Lucas S, et al. Shining a light on awareness: a review of functional near-infrared spectroscopy for prolonged disorders of consciousness. Front Neurol. 2018;Article 350:5–6.
[115] Ono T, Shindo K, Kawashima K, et al. Brain-computer interface with somatosensory feedback improves functional recovery from severe hemiplegia due to chronic stroke. Front Neuroeng. 2014;7:19.
[116] Allison B, Faller J, Neuper C. BCIs that use steady-state visual evoked potentials or slow cortical potentials. In: Jonathon R Wolpaw, Elizabeth Winter Wolpaw, editors. Brain–computer interfaces: principles and practice. Oxford, UK: Oxford University Press; 2012.
[117] Christoph G, Brendan A, Bernhard G, et al. How many people could use an SSVEP BCI? Front Neurosci. 2012;6:5–6.
[118] Han CH, Kim YW, Kim DY, *et al.* Electroencephalography-based endogenous brain–computer interface for online communication with a completely locked-in patient. J Neuroeng Rehabil. 2019;16(1):18.
[119] Li T, Zhang J, Xue T, et al. Development of a Novel Motor Imagery Control Technique and Application in a Gaming Environment. Comput Intell Neurosci. 2017;2017:5863512, 16 pages.
[120] Axmacher N, Leszczynski M, Fell J. Cross-frequency coupling and memory. Abstracts/Clinical Neurophysiology 127 (2016) e29, Tzvetan Popov, Ole Jensen, Jan-Mathijs Schoffelen. Dorsal and ventral cortices are coupled by cross-frequency interactions during working memory. NeuroImage. 2018;178:277–286.
[121] Jo HG, Naranjo JR, Hinterberger T, et al. Phase synchrony in slow cortical potentials is decreased in both expert and trained novice meditators. Neurosci Lett. 2019 May 14;701: 142–145.
[122] Birbaumer N. Slow cortical potentials: plasticity, operant control, and behavioral effects. Neuroscientist. 1999;5(2):74–78.
[123] Birbaumer N, Elbert T, Canavan AG, et al. Slow potentials of the cerebral cortex and behavior. Physiol Rev. 1990;70(1):2.
[124] Ute Strehl, Pascal Aggensteiner, Daniel Wachtlin, Daniel Brandeis, Bjorn Albrecht, Maria Arana, Christiane Bach, Tobias Banaschewski, Thorsten Bogen, Andrea Flaig-Rohr, Christine M. Freitag, Yvonne Fuchsenberger, Stephanie Gest, Holger Gevensleben, Laura Herde, Sarah Hohmann, Tanja Legenbauer, Anna-Maria Marx, Sabina Millenet, Benjamin Pniewski, Aribert Rothenberger, Christian Ruckes, Sonja Worz and Martin Holtmann. Neurofeedback of slow cortical potentials in children with attention-deficit/hyperactivity disorder: a multicenter randomized trial controlling for unspecific effects. Front Hum Neurosci. 2017;11; pp 12–13.
[125] Hasslinger J, D'Agostini Souto M, Folkesson Hellstadius L, et al. Neurofeedback in ADHD: a qualitative study of strategy use in slow cortical potential training. PLOS ONE. 2020;15(6):e0233343.
[126] Birbaumer N. Slow cortical potentials: plasticity, operant control, and behavioral effects. Neuroscientist. 1999;5(2):77.
[127] Tort ABL, Scheffer-Teixeira R, Souza BC, et al. Theta-associated high-frequency oscillations (110–160Hz) in the hippocampus and neocortex. Prog Neurobiol. 2013 Jan;100:1–14. doi: 10.1016/j.pneurobio.2012.09.002
[128] Tort ABL, Scheffer-Teixeira R, Souza BC, et al. Theta-associated high-frequency oscillations (110–160Hz) in the hippocampus and neocortex. Prog Neurobiol. 2013;100:6.
[129] Alkawadri R, Gaspard N, Goncharova II, et al. The spatial and signal characteristics of physiologic high frequency oscillations. Epilepsia. 2014 Dec;55 (12):1986–1995.
[130] Tort AB, Scheffer-Teixeira R, Souza BC, et al. Theta-associated high-frequency oscillations (110-160Hz) in the hippocampus and neocortex. Prog Neurobiol. 2013 Jan;100:1–14.
[131] Axmacher N, Elger CE, Fell J. Ripples in the medial temporal lobe are relevant for human memory consolidation. Brain. 2008;131(7):1806–1817.
[132] Frauscher B, von Ellenrieder N, Zelmann R, et al. High-frequency oscillations in the normal human brain. Ann Neurol. 2018;84(3):374–385.
[133] Ole Jensen LL. Colgin, Cross-frequency coupling between neuronal oscillations. Trends Cogn Sci. 2007;11(7):267–269.
[134] Viktor J, Viktor M. Cross-frequency coupling in real and virtual brain networks. Front Comput Neurosci. 2013;7:1.
[135] Roux F, Uhlhaas PJ. Working memory and neural oscillations: α-γ versus θ-γ codes for distinct WM information? Trends Cogn Sci. 2014;18(1):16–25.
[136] Munia TTK, Aviyente S. Time-frequency based phase-amplitude coupling measure for neuronal oscillations. Sci Rep. 2019;9(1):12441.

[137] Yousef S, Anderson William S. Cross-frequency coupling based neuromodulation for treating neurological disorders. Front Neurosci. 2019;13:1.
[138] Valencia M, Alegre M, Vicente R, et al. Cross-frequency coupling. Basic principles and measurements. Clin Neurophysiol. 2016;127(3):3.
[139] Bagur S, Benchenane K. The theta rhythm mixes and matches gamma oscillations cycle by cycle. Neuron. 2018;100(4):768–771.
[140] Grooms JK, Thompson GJ, Pan WJ, et al. Infraslow electroencephalographic and dynamic resting state network activity. Brain Connect. 2017;7(5):265–280.
[141] Lakatos P, Shah AS, Knuth KH, et al. An oscillatory hierarchy controlling neuronal excitability and stimulus processing in the auditory cortex. J Neurophysiol. 2005 Sep;94(3):1904–1911.
[142] Siebenhühner F, Wang SH, Arnulfo G, et al. Genuine cross-frequency coupling networks in human resting-state electrophysiological recordings. PLoS Biol. 2020;18(5):5.
[143] Aru J, Aru J, Priesemann V, et al. Untangling cross-frequency coupling in neuroscience. Curr Opin Neurobiol. 2015;31:51–61.
[144] Hughes C, Herrera A, Gaunt R, et al. Bidirectional brain-computer interfaces. Handb Clin Neurol. 2020;168:163–181.
[145] Benvenuto A, Raspopovic S, Hoffmann KP, et al. Intrafascicular thin-film multichannel electrodes for sensory feedback: evidences on a human amputee. Annu Int Conf IEEE Eng Med Biol Soc. 2010;2010:1800–1803.
[146] Mussa-Ivaldi FA, Miller LE. Brain–machine interfaces: computational demands and clinical needs meet basic neuroscience. Trends Neurosci. 2003;26(6):331.
[147] Bosking WH, Beauchamp MS, Yoshor D. Electrical stimulation of visual cortex: relevance for the development of visual cortical prosthetics. Annu Rev Vis Sci. 2017 Sep 15;3(1):141–166.
[148] Chuang AT, Margo CE, Greenberg PB. Retinal implants: a systematic review. Br. J. Ophthalmol. 2014;98(7):852–856.
[149] Mills JO, Jalil A, Stanga PE. Electronic retinal implants and artificial vision: journey and present. Eye (Lond). 2017;31(10):1383–1398.
[150] Manfredi G, Colombo E, Barsotti J, et al. Photochemistry of organic retinal prostheses. Annu Rev Phys Chem. 2019;70(1):99–121.
[151] Chenais NAL, Airaghi Leccardi MJI, Ghezzi D. Photovoltaic retinal prosthesis restores high-resolution responses to single-pixel stimulation in blind retinas. Commun Mater. 2021;2(1):28.
[152] Klaes C, Shi Y, Kellis S, et al. A cognitive neuroprosthetic that uses cortical stimulation for somatosensory feedback. J Neural Eng. 2014 Oct;11(5):056024.
[153] Caldwell DJ, Cronin JA, Wu J, et al. Direct stimulation of somatosensory cortex results in slower reaction times compared to peripheral touch in humans. Sci Rep. 2019;9(1):3292.
[154] Mazurek KA, Schieber MH. Injecting Information into the Mammalian Cortex: progress, challenges, and promise. Neuroscientist. 2021 Apr;27(2):130–132.
[155] Flesher SN, Collinger JL, Foldes ST, et al. Intracortical microstimulation of human somatosensory cortex. Sci Transl Med. 2016 Oct 19;8(361):361ra141.
[156] Zeng H, Wang Y, Wu C, et al. Closed-loop hybrid gaze brain-machine interface based robotic arm control with augmented reality feedback. Front Neurorobot. 2017;11:60.
[157] Collinger JL, Wodlinger B, Downey JE, et al. High-performance neuroprosthetic control by an individual with tetraplegia. Lancet. 2013;381(9866):557–564.
[158] Quick KM, Weiss JM, Clemente F, et al. Intracortical microstimulation feedback improves grasp force accuracy in a human using a brain-computer interface. Annu Int Conf IEEE Eng Med Biol Soc. 2020;2020:3355–3358.
[159] Flesher SN, Downey JE, Weiss JM, et al. A brain-computer interface that evokes tactile sensations improves robotic arm control. Science. 2021 May 21;372(6544):831–836.
[160] Caldwell David J, Ojemann Jeffrey G, Rao Rajesh PN. Direct electrical stimulation in electrocorticographic brain–computer interfaces: enabling technologies for input to cortex. Front Neurosci. 2019;13:3.
[161] Mazurek KA, Schieber MH. injecting information into the mammalian cortex: progress, challenges, and promise. Neuroscientist. 2021 Apr;27(2):129–142.
[162] Boulay CB, Sarnacki WA, Wolpaw JR, et al. Trained modulation of sensorimotor rhythms can affect reaction time. Clin Neurophysiol. 2011;122(9):1820–1826.
[163] Millán José del R, Rüdiger R, Gernot M-P, et al. combining brain–computer interfaces and assistive technologies: state-of-the-art and challenges. Front Neurosci. 2010;4; 9–10.
[164] Guggenmos DJ, Azin M, Barbay S, et al. Restoration of function after brain damage using a neural prosthesis. Proc Natl Acad Sci USA. 2013;110(52):21177–21182.
[165] George R, Chiappalone M, Giugliano M, et al. Plasticity and adaptation in neuromorphic biohybrid systems. iScience. 2020;23(10):101589.
[166] Kennedy PR, Bakay RAE, Moore MM, et al. Direct control of a computer from the human central nervous system. IEEE Trans Neural Syst Rehabil Eng. 2000;8(2):198–202.
[167] Mussa-Ivaldi FA, Miller LE. Brain–machine interfaces: computational demands and clinical needs meet basic neuroscience. Trends Neurosci. 2003;26(6):330.
[168] Collinger JL, Wodlinger B, Downey JE, et al. High-performance neuroprosthetic control by an individual with tetraplegia. Lancet. 2013;381(9866):562.
[169] Marchesotti S, Martuzzi R, Schurger A, et al. Cortical and subcortical mechanisms of brain-machine interfaces. Hum Brain Mapp. 2017 Jun;38(6):2971–2989.
[170] Kropotov JD. Chapter 4.5 "Transcranial magnetic stimulation" in functional neuromarkers for psychiatry. Academic Press; Boston, Massachusetts, USA; 2016. p. 59.

[171] Pels EGM, Aarnoutse EJ, Leinders S, et al. Stability of a chronic implanted brain-computer interface in late-stage amyotrophic lateral sclerosis. Clin Neurophysiol. 2019;130(10):1798–1803.
[172] Szarowski DH, Andersen MD, Retterer S, et al. Brain responses to micro-machined silicon devices. Brain Res. 2003;983(1–2):23–35.
[173] Hong G, Viveros RD, Zwang TJ, et al. Tissue-like neural probes for understanding and modulating the brain. Biochemistry. 2018;57(27):3997.
[174] Rizzi G, Scrivani A, Fini M, et al. Biomedical coatings to improve the tissue-biomaterial interface. Int J Artif Organs. 2004;27(8):649–657.
[175] Bowen J, Chaofan G, Guo Z, et al. Flexible and stretchable opto-electric neural interface for low-noise electrocorticogram recordings and neuromodulation in vivo. Biosens Bioelectron. 2020;153. DOI:10.1016/j.bios.2020.112009.
[176] Fekete Z, Pongrácz A. Multifunctional soft implants to monitor and control neural activity in the central and peripheral nervous system: a review. Sens Actuators B Chem. 2017;243:1214–1223.
[177] Axpe E, Orive G, Franze K, et al. Towards brain-tissue-like biomaterials. Nat Commun. 2020;11(1):3423.
[178] Hong G, Viveros RD, Zwang TJ, et al. Tissue-like neural probes for understanding and modulating the brain. Biochemistry. 2018;57(27):3995–4004.
[179] Hong G, Yang X, Zhou T, et al. Mesh electronics: a new paradigm for tissue-like brain probes. Curr Opin Neurobiol. 2018;50:33.
[180] Mazurek KA, Schieber MH. injecting information into the mammalian cortex: progress, challenges, and promise. Neuroscientist. 2021;27(2):139.
[181] Jiang X, Bian GB, Tian Z. Removal of artifacts from EEG signals: a review. Sensors (Basel). 2019 Feb 26;19(5):987.
[182] Yılmaz G, Ungan P, Sebik O, et al. Interference of tonic muscle activity on the EEG: a single motor unit study. Front Hum Neurosci. 2014;8:504.
[183] Birbaumer N, Elbert T, Canavan A, et al. Slow Potentials of the Cerebral Cortex and Behavior. Physiol Rev. 1990;70(1):10–11.
[184] Creel DJ "VEP recording methods". in visually evoked potentials. Webvision. Moran Eye Center, Nov 29, 2020. http://webvision.med.utah.edu/book/electrophysiology/visually-evoked-potentials ;accessed 20 May 2021.
[185] Hinrichs H, Scholz M, Baum AK, et al. Comparison between a wireless dry electrode EEG system with a conventional wired wet electrode EEG system for clinical applications. Sci Rep. 2020;10(1):5218.
[186] Zhang L, Kumar KS, He H, et al. Fully organic compliant dry electrodes self-adhesive to skin for long-term motion-robust epidermal biopotential monitoring. Nat Commun. 2020;11(1):4683.
[187] Fenoy AJ, Simpson RK Jr. Risks of common complications in deep brain stimulation surgery: management and avoidance. J Neurosurg. 2014 Jan;120(1):132–139.
[188] Fenoy AJ, Simpson RK Jr. Management of device-related wound complications in deep brain stimulation surgery. J Neurosurg. 2012 Jun;116(6):1324–1332.
[189] Dimiter P, Jean D. Mechanical and biological interactions of implants with the brain and their impact on implant design. Front Neurosci. 2016;10:4.
[190] Polikov VS, Tresco PA, Reichert WM. Response of brain tissue to chronically implanted neural electrodes. J Neurosci Methods. 2005;148(1):1–18.
[191] Mowla M Rakibul, Huggins J E, Thompson David E. Enhancing P300-BCI performance thorugh latency estimation. Brain-Computer Interfaces. 2017;4(3):137–145.
[192] Lugo ZR, Pokorny C, Pellas F, et al. Mental imagery for brain-computer interface control and communication in non-responsive individuals. Ann Phys Rehabil Med. 2020;63(1):21–27.
[193] Blankertz B, Sannelli C, Sebastian Halder EM, et al. Neurophysiological predictor of SMR-based BCI performance. NeuroImage. 2010;51(4):1303–1309.
[194] Emami Z, Chau T. The effects of visual distractors on cognitive load in a motor imagery brain-computer interface. Behav Brain Res. 2020;378:112240.
[195] Fekete Z, Németh A, Márton G, et al. Experimental study on the mechanical interaction between silicon neural microprobes and rat dura mater during insertion. J Mater Sci Mater Med. 2015;26:70.
[196] O'Connell RG, Balsters JH, Kilcullen SM, et al. A simultaneous ERP/fMRI investigation of the P300 aging effect. Neurobiol Aging. 2012;33(10):2448–2461.
[197] Fjell AM, Rosquist H, Walhovd KB. Instability in the latency of p3a/p3b brain potentials and cognitive function in aging. Neurobiol Aging. 2009;30(12):2065–2079.
[198] Perdikis S, Tonin L, Saeedi S, et al. The Cybathlon BCI race: successful longitudinal mutual learning with two tetraplegic users. PLoS Biol. 2018;16(5):e2003787.
[199] Zisk AH, Borgheai SB, McLinden J, et al. P300 latency jitter and its correlates in people with amyotrophic lateral sclerosis. Clin Neurophysiol. 2021;132(2):632–642.
[200] Francesca Schettini, Monica Risetti, Pietro Arico, Rita Formisano, Fabio Babiloni, Donatella Mattia, Febo Cincotti. P300 latency Jitter occurrence in patients with disorders of consciousness: toward a better design for Brain Computer Interface applications. 2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC); Milan, Italy; 2015. p. 6178–6181. doi: 10.1109/EMBC.2015.7319803
[201] Mowla MR, Huggins JE, Natarajan B, et al. P300 latency estimation using least mean squares filter. Annu Int Conf IEEE Eng Med Biol Soc. 2018 Jul;2018:1976–1979.
[202] Narayanan RT, Udvary D, Oberlaender M. Cell type-specific structural organization of the six layers in rat barrel cortex. Front Neuroanat. 2017;11. DOI:10.3389/fnana.2017.00091
[203] Ioan O, Stephano C, Noga Brian R. What is the evidence for inter-laminar integration in a prefrontal cortical minicolumn? Front Neuroanat. 2017;11. p. 9. https://doi.org/10.3389/fnana.2017.00116
[204] Vassanelli S, Mahmud M, Girardi S, et al. On the way to large-scale and high-resolution brain-chip interfacing. Cogni Comput. 2012;4(1):71–81.
[205] Sempreboni D, Luca V. Privacy, security and trust in the internet of neurons; 11 July 2018. arXiv:1807.06077 [cs.CY]
[206] Mahmud M, Vassanelli S. Processing and analysis of multichannel extracellular neuronal signals: state-of-the-art and challenges. Front Neurosci. 2016;10:248.