Optical Noninvasive Brain–Computer Interface Development: Challenges and Opportunities

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ABSTRACT

The Defense Advanced Research Projects Agency's Revolutionizing Prosthetics program demonstrated the potential for neural interface technologies, enabling patients to control and feel a prosthetic arm and hand, and even pilot an aircraft in simulation. These landmark achievements required invasive, chronically implanted penetrating electrode arrays, which are fundamentally incompatible with applications for the able-bodied warfighter or for long-term clinical applications. Noninvasive neural recording approaches have not been as effective, suffering from severe limitations in temporal and spatial resolution, signal-to-noise ratio, depth penetration, portability, and cost. To help close these gaps, researchers at the Johns Hopkins University Applied Physics Laboratory (APL) are exploring optical techniques that record correlates of neural activity through either hemodynamic signatures or neural tissue motion as represented by the fast optical signal. Although these two signatures differ in terms of spatiotemporal resolution and depth at which the neural activity is recorded, they provide a path to realizing a portable, low-cost, high-performance brain–computer interface. If successful, this work will help usher in a new era of computing at the speed of thought.

INTRODUCTION

Brain–computer interface (BCI) systems consist of three distinct components: (1) a neural signal extraction technology for recording neural activity; (2) a signal processing module for converting the neural signal into features for classification or analysis; and (3) an application module that performs the desired task on a computer or by using a robotic device. The neural signal extraction technology is perhaps one of the weakest links in these systems, as all currently available noninvasive neural signal extraction technologies perform suboptimally in one or more dimensions of spatial resolution, temporal resolution, or mobility.

One of the first technologies for recording neural signals preceding the term *BCI* is arguably the electroencephalogram (EEG), which was demonstrated in 1929 by German scientist Hans Berger. In this pioneering work, Berger produced the first recording of electrical brain activity from the human scalp. It was another three decades before the first demonstration of EEG decoding from the human brain was demonstrated. Then, in

1964, William Grey Walter trained a patient to advance projector slides by merely monitoring the patient's intent to depress a button that was previously wired to advance slides.[1] In the 1970s Jacques Vidal proposed a detailed system architecture to connect a human brain with a computer system in a noninvasive multi-electrode configuration[2] that would achieve both encode and decode operations. In this early work, Vidal, who coined the term *BCI*, speculated on the use of BCI for controlling prosthetic devices and spaceships.

Since those early developments, both invasive and noninvasive BCIs have found many applications, including sensorimotor rehabilitation,[3] cognitive skills training,[4,5] imagined and overt speech decoding,[6–8] gaming,[9] and quadcopter control.[10] While the invasive BCI developments utilizing electrical recordings have shown tremendous potential for BCI, the noninvasive EEG recordings generally lack the necessary resolution and signal-to-noise ratio to achieve equally impressive results. For a more in-depth review, see the review article written largely by contractors or employees of the Defense Advanced Research Projects Agency (DARPA), an agency that began funding BCI research as early as 1974.[11] Collectively, BCIs offer the potential to enhance communicating and controlling applications in a way that does not suffer from the limited bandwidth exemplified by human speech or sequential button presses.

While this foundational BCI work utilizing invasive electrical recordings showcases many great proof-of-concept examples of how BCI can be used, it is also clear that to be universally adapted, a noninvasive BCI system must be small, lightweight, unobtrusive, easy to use (with minimal training time), energy efficient (requiring no recharging during the day), affordable, reagentless, able to provide real-time information, and adaptive to the plasticity of the human brain. This is no small task, and to date, no BCI system has been able to come close to meeting these requirements. EEG provides excellent temporal resolution, portability, and clinical relevance but at the expense of spatial resolution and signal-to-noise ratio.[11] Magnetoencephalography appears to be superior to EEG in several ways but has limited use in BCI applications primarily because of cost, size, portability, and signal clutter (extreme sensitivity to the magnetic field of the environment). More recent noninvasive recording techniques that rely on detecting hemodynamic signatures, such as functional near-infrared spectroscopy (fNIRS),[12] functional magnetic resonance imaging (fMRI), and focused ultrasound,[13] have discrete physiological limits on temporal resolution (or temporal feedback) on the order of several seconds.

The relative spatial, temporal, and mobility constraints of these and other technologies are illustrated in Figure 1 (inspired by Mehta and Parasuraman[14]). As shown in this figure, the ideal noninvasive BCI system would employ a neural signal extraction technology

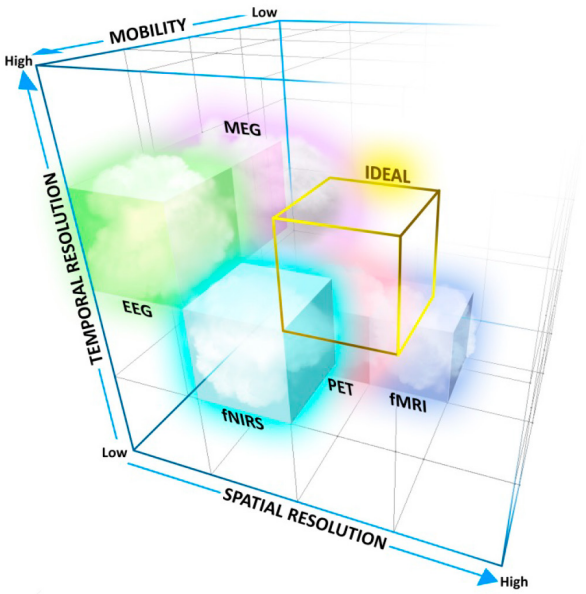

Figure 1. Comparison of existing technologies for extracting neural signals and physiological processing correlated with neural signals from the brain. Technologies are positioned in a 3-D space relative to spatial resolution, temporal resolution, and system mobility. The ideal technology would have specifications within the gold cube. Optical methods are most likely to succeed at achieving a technology in this regime. MEG, magnetoencephalography; PET, positron emission tomography. (Figure inspired by Mehta and Parasuraman,[14] whose figure is licensed under CC BY 3.0, https://creativecommons.org/licenses/by/3.0/.)

with the temporal resolution and mobility of EEG coupled with the spatial resolution of fMRI. This idealized spatiotemporal performance approaches that achieved invasively by implanting electrodes directly in the neural tissue or on the surface of the cortex, but with far more extensive spatial extent than implanted devices and no requirement to drill through the skull for implantation.

BACKGROUND

To overcome the challenges of developing a high-performance, noninvasive BCI device, APL researchers are investigating two optical approaches to decode neural activity through recording of either a hemodynamic signature or the fast optical signal (FOS). The hemodynamic signature, based on the pioneering work of Jöbsis,[15] is the most commonly used optical neural imaging approach. In 1977 Jöbsis showed the feasibility of using near-infrared light to noninvasively monitor biological hemodynamics—a response that allows oxygenated blood to be delivered to active neurons. Several decades later, in 2004 Coyle et al.[16] demonstrated the feasibility of using fNIRS for BCI applications. The concept of functional neural imaging using fNIRS is based on the change in optical absorption that accompanies

the hemodynamic response associated with task-evoked activation.[17] Typically, fNIRS systems are designed to interrogate the spectroscopic change in absorption of hemoglobin, which has an isosbestic point near a wavelength of 800 nm; measuring above and below this wavelength and applying the modified Beer–Lambert law enables calculation of concentrations of oxygenated and deoxygenated hemoglobin. Tomographic reconstruction of fNIRS, also known as diffuse optical tomography (DOT), can be performed based on assumptions of the anatomical structure of the region of interest.

Recent work on high-density DOT (HD-DOT) has shown the advantages of using densely spaced transmit and receive pairs to enhance the spatial resolution over earlier sparse approaches.[18–20] Several studies analyzed the spatial correspondence with other modalities, with promising results[21] including correspondence as close as 4.4 ± 1 mm between fMRI and HD-DOT.[22] The optical depth of penetration depends on the configuration of the fNIRS system. Continuous-wave approaches that collect diffuse photons can only operate in a canonical transmit–receive detection scheme, in which the only available method to increase depth is to increase the distance between the transmitter and receiver. In contrast, time-domain approaches that employ pulsed light sources can collect photons in a null transmit–receive configuration, which has limited dependence on the distance between the transmitter and the receiver. Therefore, in time-domain approaches the average depth reached by a photon is directly related to the average time spent inside the tissue. Depth of penetration in the brain has been modeled to be as large as 6 cm when time-gating approaches are proposed.[23] To date, tomographic reconstruction methods have demonstrated volumetric resolution on the order of 1 cm^3 with temporal resolution limited by the relatively slow response of the hemodynamic waveform that peaks about 3–5 s after the onset of neural activity.

In addition to the hemodynamic signal, the FOS is another optical signal that holds potential for noninvasive BCI. Some researchers have described the FOS as a measure of discriminable neural features, but many aspects of the FOS remain controversial[24]—it is not even entirely clear which specific biological process the FOS captures. This controversy is highlighted by contradictory results in the FOS literature encompassing both positive and negative results, summarized by Torricelli et al.[24] A critical challenge in observing the FOS is that it is extremely localized and weak, with scattering changes in the cortex estimated to have magnitudes much smaller than 0.4%.[25]

What is known is that during neural activity, a cascade of cellular and metabolic events transpires when an excitable cell produces an action potential. These events include sodium (Na^+) and potassium (K^+) ion movement across cell membranes, opening of voltage-gated ion channels in response to depolarization, an influx of calcium ions (Ca^{2+}) at synapses causing vesicles to fuse with the cell membrane, neurotransmitter release from vesicles into the synaptic cleft, neurotransmitter binding to receptor molecules on the postsynaptic membrane, conformational changes in ion channels on the postsynaptic cleft, postsynaptic currents altering the excitability of the postsynaptic cell, retrieval of vesicular membrane from the plasma membrane in the presynaptic neuron, and neurotransmitter synthesis in stored vesicles in the presynaptic membrane.[26] The FOS is attributed to any change in scattering properties or motion of brain tissue concurrent to neural activity in the tissue. What makes this exciting is that it is believed to occur on spatiotemporal scales concurrent to localized populations of neural activity (tens to hundreds of milliseconds),[27] as conceptually illustrated in the middle panel of Figure 2. Such changes in scattering properties of tissue have been observed across a variety of experimental preparations, including individual axons,[28] brain slices,[29] and depth recordings in vivo.[30] Because of the tightly coupled origin between the FOS and neural activity, the FOS is hypothesized to be highly correlated with electrical measures of neural activity such as the local field potential, which is detected by an electrode located on or in neural tissue.

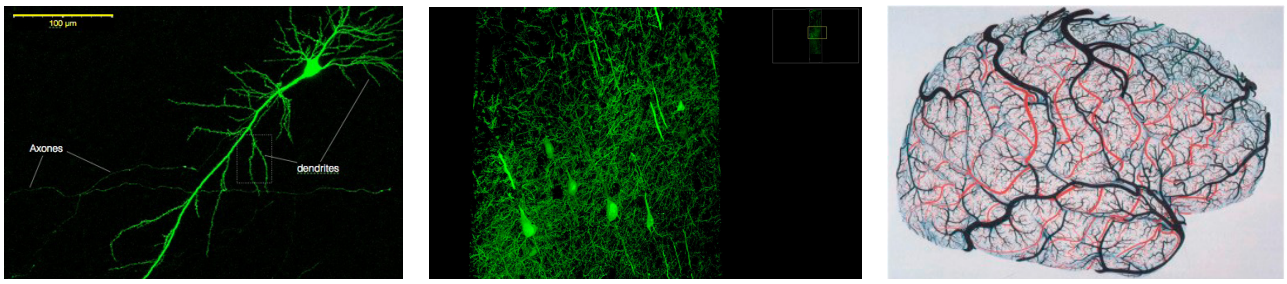

Figure 2. Comparison of intrinsic recording volume/scale. The scale ranges from a single neuron (left), a population of neurons inducing changes in optical properties represented by the FOS (middle), to hemodynamic responses recorded from the vascular network across the surface of the cortex (right). (Left, by Mathias De Roo, CC BY-SA 3.0, https://creativecommons.org/licenses/by-sa/3.0, via Wikimedia Commons; middle, by dan.oshea, licensed under CC BY-NC-SA 2.0, https://creativecommons.org/licenses/by-nc-sa/2.0/, via Flickr; right, reprinted from Duvernoy, Delon, and Vannson[31] with permission from Elsevier.)

From a system design standpoint, both of these optical approaches for BCI applications have the potential for high spatial and temporal resolution, low cost, and the ability to operate outside of traditional clinical settings. APL researchers are working to realize the potential of these two design approaches.

BCI DESIGN APPROACH

The fundamental neurobiological hypothesis being tested is whether we can build an optical system that can noninvasively measure changes in the brain tissue's properties that correlate directly to neural activity. The first of these systems leverages the hemodynamic signature, which is relatively well understood, while the second focuses on recording the FOS and requires more fundamental research on the characteristics of the signature itself before the transition to human subject testing can even begin. The greatest challenge in developing an optical system is accounting for the significant amount of optical scatter that occurs as light propagates through tissue. As shown in Figure 3, neural tissue is a highly scattering medium that divides the light into diffuse, "snake" (or quasi-ballistic), and ballistic components. Diffuse light, termed incoherent light, is the result of the light experiencing multiple scattering events within the medium, and is the largest component of the light that propagates through tissue. Diffuse light experiences many scattering events and migrates through the tissue in a variety of tortuous paths, making it unsuitable for conventional imaging applications (i.e., an image cannot be formed with diffusely scattered light). However, the optical properties (and dynamic changes of the optical properties) of the medium through which the light propagates in a diffuse fashion can still be measured. In comparison, ballistic and snake, or quasi-ballistic, light are descriptive of coherent light, light that has either remained unscattered or only minimally scattered. Coherent light, in contrast to incoherent light, maintains information on an object it encounters and is therefore well suited for conventional imaging analysis. The challenge in leveraging these coherent components is that they represent only a small portion of the total light that propagates through tissue, making it difficult to separate them from the diffuse, or incoherent, component.

APL researchers are developing advanced optical imaging systems that rely on accurate recording and processing of diffuse and coherent light, respectively. Success is based on the ability to bring together a suitably diverse team that includes neuroscientists, electrical engineers, optical scientists, and physics-based modelers to advance what can be achieved in academic labs or commercial entities.

fNIRS System Development and Results for Diffuse Optical Imaging

As stated previously, many groups are pursuing fNIRS approaches for BCI, but APL has been particularly active in pushing forward diffuse imaging technologies with the goal of achieving robust, high-resolution measurements of neural tissue properties. The high-level research question that drives this work is simple: How much information can be recorded from a subject's brain using noninvasive techniques? In more precise terms, our team benchmarks current imaging technologies (e.g., continuous-wave fNIRS) and then studies how advances in more nascent approaches such as frequency- and time-domain fNIRS can improve on those results. The amount of neural information that can be obtained is discussed using the broad mathematical framework developed for information content or signal dimensionality. The core motivation for developing diffuse imaging systems with improved spatial resolution is that these cutting-edge diffuse imaging systems are able to achieve higher dimensionality because they can differentiate neural activation originating from nearby volumes in the brain.

Research has demonstrated that the quality of DOT image reconstruction is improved by incorporating phase shift measurements assessed using frequency-domain fNIRS in addition to traditional intensity changes measured using continuous-wave fNIRS.[31] However, APL is continuing to push the bounds on

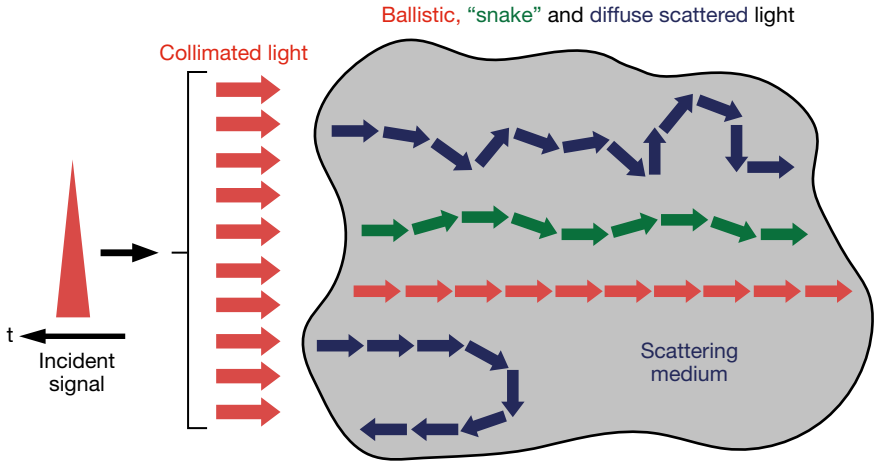

Figure 3. Breakdown of light. Light is divided into ballistic, snake, and diffuse components as it propagates through a highly scattering medium such as tissue. (From Dunsby and French.[32] © IOP Publishing. Reproduced with permission. All rights reserved.)

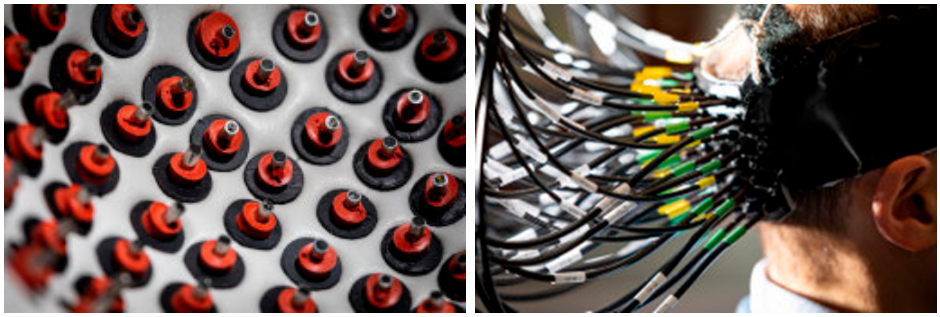

Figure 4. Example of an optical-fiber-based head cap for diffuse optical imaging of the brain.

what can be achieved using noninvasive diffuse imaging through research thrusts in time-domain fNIRS systems. These approaches incorporate higher-precision time-of-flight information using pulsed lasers and photon-counting electronics. To date, researchers perform measurements using head caps such as the one shown in Figure 4, where optical fiber is used to both transmit the light into the head and detect the light after propagating through the neural tissue. In the future, the community must develop wearable technologies to move experiments out of optics laboratory suites, as well as more advanced neuroscience approaches that may someday allow patients to learn to use a BCI in a manner that mirrors how one might learn a new spoken language today.

FOS System Development and Results for Coherent Optical Imaging

Digital holographic imaging (DHI) leverages the coherent light (ballistic and quasi-ballistic) to enable the formation of a complex image (i.e., optical magnitude and phase). This interferometric approach, used in a wide variety of applications ranging from metrology to stress/strain measurements and biological imaging, enables the optical phase to be measured, which provides sub-wavelength sensitivity to axial motion of the sample. At near-infrared wavelengths, motion sensitivity on the order of tens of nanometers can be achieved, which is well matched to the motion of tissue induced by neural activity. While many published experiments that aimed at confirming the existence and investigating the origin of the FOS used similar interferometric techniques, most of the systems used in these experiments were developed for ex vivo and in vitro samples and do not translate for in vivo measurements. It is this key observation that drives APL's development of DHI for neural activity detection—the need to make phase-based measurements in highly dynamic, volumetric in vivo biological systems.

With this driving function, APL's DHI system for BCI has evolved over several years through benchtop and in vivo experimentation designed to hone the system's sensitivity to tissue motion attributable to neural activity. Challenges related to the inherent motion of tissue due to blood perfusion and other physiological signatures such as heart rate and breathing have been addressed through careful system design and optimization. The resulting DHI sensor provides a pathway for noninvasive detection of neural activity with spatiotemporal resolutions approaching that of invasive techniques.

With the success of the in vivo measurements, the APL team is preparing to transition to human subject testing. These tests will present new challenges in first understanding, at the fundamental level, how the neural activity signals differ between rodents and humans and then understanding how to make these very precise neural tissue motion measurements through the human scalp and skull.

DISCUSSION

Next-generation noninvasive BCI systems have the potential to bring assistive and rehabilitative devices to broader audiences as well as to unleash entirely new modes of human–computer interaction. There is tremendous value in working with patients who can provide invasive brain access allowing research teams to explore and optimize the underlying desired functionalities. If a desired functionality can be achieved invasively, this serves as a proof-of-concept demonstration for pursuing similar functionality noninvasively. The goal, then, is to develop a noninvasive BCI method, with spatiotemporal resolution that rivals that of invasive techniques, to directly capture neuronal activity from a variety of cortical neuronal populations. Both hemodynamic measures using fNIRS and FOS measured with DHI are able to achieve some of these desired system requirements already, and we believe that through advanced system development both will move closer to achieving performance similar to that of invasive BCI technology. Significant challenges remain in miniaturizing enabling components, but advances in integrated circuits and photonics should allow these systems to meet the criteria for a successful, deployable noninvasive BCI system: small form factor, lightweight, easy to use, energy efficient, affordable, able to operate in real time and without reagents, and adaptive to neural plasticity.

ACKNOWLEDGMENTS: This material is based on work supported by APL under an independent research and development project.

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