A Survey of Technologies for Brain Computer Interface Developments to Treat Neuropsychiatric Disorders

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Abstract

Neuropsychiatric disorders are a huge cause of global disability. Despite decades of research little progress has been made on effective treatments for many of these disorders. Brain-computer interfacing (BCI) is a method that allows for a close integration between computer interfaces and functional brain activation. It is currently under investigation to work as a neuroprosthetic to restore vision, hearing and muscle movement. Further development of BCI technologies have the potential to alter the approach taken with regard to the treatment of neuropsychiatric disorders, and may greatly improve the quality of life for many individuals suffering from currently untreatable disorders, such as Alzheimer's disease, Parkinson's disease or treatment resistant depression. This article will address what criteria are of importance for effective implementation of BCI in the treatment of different neuropsychiatric disorders, and will provide an overview of the different types of brain computer interfaces that are under development. It will conclude with an overview of limitations and future directions of BCI technologies.

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MEDICINE

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DO TROMP

Neuropsychiatric disorders are a huge cause of global disability. Despite decades of research little progress has been made on effective treatments for many of these disorders. Brain-computer interfacing (BCI) is a method that allows for a close integration between computer interfaces and functional brain activation. It is currently under investigation to work as a neuroprosthetic to restore vision, hearing and muscle movement. Further development of BCI technologies have the potential to alter the approach taken with regard to the treatment of neuropsychiatric disorders, and may greatly improve the quality of life for many individuals suffering from currently untreatable disorders, such as Alzheimer's disease, Parkinson's disease or treatment resistant depression. This article will address what criteria are of importance for effective implementation of BCI in the treatment of different neuropsychiatric disorders, and will provide an overview of the different types of brain computer interfaces that are under development. It will conclude with an overview of limitations and future directions of BCI technologies.

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BACKGROUND

Neuropsychiatric disorders are the number one cause of disability in the United States, and rank third globally (Murray et al. 2012; Whiteford et al. 2013; Murray 2013). Although treatments are available for many disorders, a significant number of patients remain treatment resistant (Keller 1992; Fava 2003; Rush et al. 2006), or suffer from serious side effects (Bystritsky et al. 2013). These issues have become the focus of the National Institute of Mental Health and their director who has remarked that: "*There has been no major innovation in therapeutics for most mental disorders since 1960. Current treatments are not good enough for too many*." Thomas Insel (Insel 2012). Highlighting the need for drastic changes in the approach to the development of novel treatments for psychiatric disorders.

Progress in this field is complicated by the immense intricacy of the human brain, containing over 100 billion neurons, many trillions of synaptic connections, and many hundreds of different cell types (Adolphs 2015). These connections together compose a unique connectome that is shaped by individual differences in genetic and environmental circumstances (Lichtman, Pfister, and Shavit 2014). It is becoming increasingly clear that there is not one single genetic cause, nor a single dysregulated brain region that stands at the root of any psychopathology. Instead we are beginning to understand that psychopathology can develop through a large number of genetic pathways and distributed brain networks (Akil et al. 2010; Fox and Kalin 2014). Kay Tye notes that shifting the focus to circuit level therapeutics will significantly transform the quality of mental health care (Tye 2014). Novel treatments will have to modulate these distributed networks in as of yet unknown ways (Tye 2014). To achieve neuromodulation of these distributed brain regions an important yet under-appreciated candidate includes brain computer interfacing (BCI).

So far most efforts to understand the psychophysiology of mental disorders have focused on one of two modes of discovery; they either aimed to measure brain function (e.g. through electric encephalograms [EEG] or functional magnetic resonance imaging [fMRI]) or they tried to modulate

activity in the brain (e.g. through transcranial magnetic stimulation [TMS] or deep brain stimulation [DBS]). Few efforts so far have attempted to combine measuring brain activity with adaptive modulation, to allow for a neuromodulatory feedback loop, or closed-loop system (Grosenick, Marshel, and Deisseroth 2015). BCI is a method that allows for a close integration between a computer interface, brain measurements and brain modulation.

An important current application of BCI is as a neuroprosthetic, to help restore or substitute a motor, sensory or cognitive modality. An excellent example is the use of cochlear implants in individuals with hearing loss due to damaged transmission of sound to the cochlear. Cochlear implants register proximal sounds using an external microphone, and transmits that sound to the auditory nerve using a micro-electrode array, achieving unprecedented recovery of hearing ability (Wilson and Dorman 2008). This is just one example of the application of BCI, there are many others in development and under investigation at different research centers. For example, one group at the University of California, Los Angeles has been able to induce voluntary movement using spinal cord stimulation in 4 patients suffering from complete motor paralysis (Angeli et al. 2014). The commercial company Second Sight Medical Products recently received FDA approval for a retinal implant to help individuals suffering from advanced retinitis pigmentosa. Furthermore, the Defense Advanced Research Projects Agency (DARPA), has projects that are exploring the potential of BCI in prosthetics, brain injury recovery, sensory motor function recovery and memory encoding restoration (Miranda et al. 2014).

The question now remains if novel developments in this field have advanced far enough such that BCI can be safely applied in human populations to treat neural and psychiatric disorders. This manuscript will describe the criteria that BCI needs to fulfill in order to be considered viable as a treatment for neuropsychiatric disease. It will then discuss what neural interfaces are currently available or in development, and how these interfaces measure up with regard to the criteria described. Finally, it will address the future directions and limitations.

CRITERIA

In order to find the methods with the greatest potential to alter the current treatment of psychopathology a number of criteria need to be established. These criteria will help determine if any of the described techniques are ready, or likely to become ready, to help with the develop of novel treatments, or become itself a course of treatment. I will describe the main criteria that I think are of importance to established if neural interfaces have the potential to be effective in the treatment of psychiatric illness.

READ & WRITE INTERFACE

The most important criteria for the implementation as treatment is that it should enable a neural interface, where it will either measure; “read”, modulate; “write”, or preferably do both. This technique can enable an interface between an advanced computing power and the brain. Practically this would mean that the brain and the computer are connected by a device or “hub”. A sub-unit of the hub should be able to read the activity levels of local neurons and relay that information to the computer. Ideally the computer can then calculate how this activity differs from the objective for this specific neural cluster. Next, the system can then in turn send data to the hub, which it will translated to a signal that can either activate or inhibit local populations of neurons. This way the computing system has the ability to influence the neural system towards an objective goal. An optimal form of this system can be considered a closed-loop system, where neural perturbations can be measured, adjusted and measured again, in order to achieve a target outcome (Grosenick, Marshel, and Deisseroth 2015). This target goal can range from neural level objectives to mood or behavioral alterations.

TEMPORAL & SPATIAL RESOLUTION

An important condition for effective neural interfacing is temporal resolution. A system can only be effective when it has a high temporal sensitivity, where signals can be read and written at less than

millisecond level (<0.1ms). As Grosenick *et al.* (Grosenick, Marshel, and Deisseroth 2015) put it: "*In particular, observing and feeding back the effects of circuit interventions on physiologically relevant timescales is valuable for directly testing whether inferred models of dynamics, connectivity, and causation are accurate in vivo.*". In a practical sense, in order to effectively decode neural signal to synthesize the underlying output, like speech or motor movement a high level of precision will be necessary (Kennedy 2012). Furthermore, adequate temporal resolution is important in order to effectively modulate ongoing neural signals in the brain. Since correct timing is highly important for the effective integration of the external signal into ongoing neural processing.

Beyond temporal resolution, the level of spatial resolution is of major importance in order to target neural populations of interest. Any method with larger than sub-millimeter (mm) resolution runs the risk of activating populations of neurons that belong to different networks or different systems, thus causing unintended effects, or non specificity. While only influencing a few neurons will likely often be insufficient to effectively influence the targeted behavior. These spatial parameters can also be described in binary pattern recognition terms. For the BCI system to effectively alter a highly specialized activity like psychosocial behavior it will have to modulate brain activity with high spatial specificity and sensitivity. This means that not just whole brain regions should be influenced indiscriminately, but specific cell types within specific brain regions are targeted on the neuron to dendrite level (< 0.01 mm). This can be referred to as the *precision* of the system to reliably filter the signal specific for the goal (green in Figure 1) from the noise of the rest of the brain (red Figure 1).

In addition, the BCI system has to effectively measure enough of the neuronal activity to effectively influence or read what behavior is taking place. As described in Schwarz *et al.*, the efficacy of BCI systems to predict behavior from neuronal activity "*increases linearly with the logarithm of the cortical neuronal sample recorded simultaneously*" (Schwarz et al. 2014). This can also be described as *sensitivity*; the number of relevant items (green in Figure 1) that are selected from the total of available relevant elements (gray in Figure 1). This is not only the case for measuring behavior, but is similarly true for modulating behavior. A sufficiently large sample of neurons has to be influenced to effectively modulate behavior. Furthermore, it is likely that influencing a single brain region will be insufficient to alter complex emotional and learned behaviors. Nor is it likely that influencing the readily accessible cortex will be sufficient to significantly alter complex behavioral systems that are based on multi-sensory integration in the deeper limbic system.

The introduction of optogenetic methods has helped elucidate that the activation of populations of synapses is insufficient to change learned behaviors and instead ensembles of neurons are necessary to induce behavioral alterations (Tye 2014). These target neuronal ensembles are most likely distributed throughout both cortical and sub-cortical regions (Fox et al. 2015). To effectively target these distributed circuits neural interfaces will need to include at least a number of distributed hubs that can each individually influence their local environment. As technology progresses these hubs may become progressively smaller and can increase in number and potentially over time become distributed throughout the entire brain.

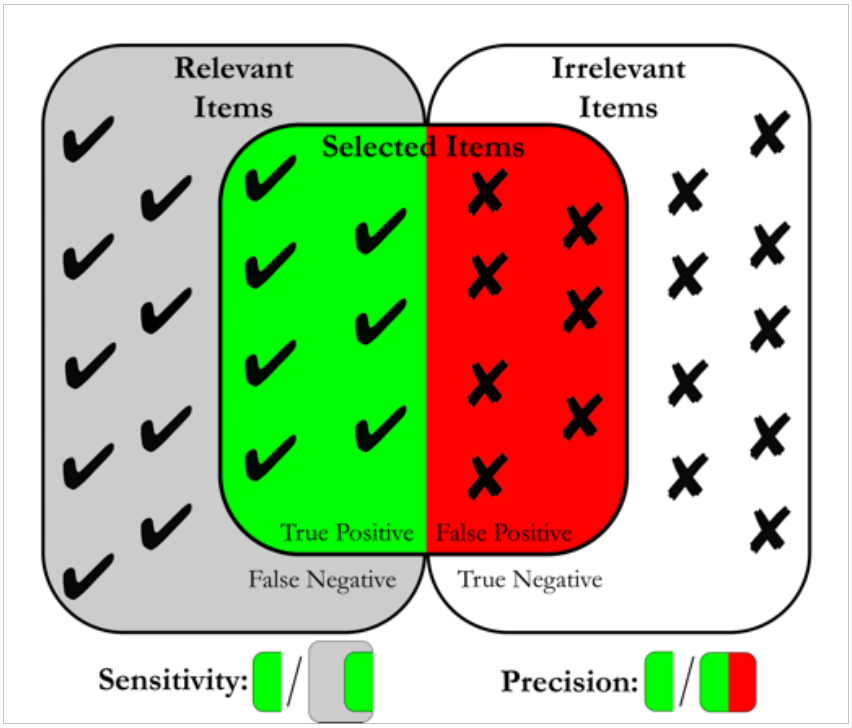

Figure 1: Sensitivity & Precision. Sensitivity is defined as the proportion of relevant items that are selected. Precision is the proportion of selected items that are relevant.

SAFETY

It is important that the system is minimally invasive, to ensure health and safety of the participant. This means that the probability of brain lesions, neural death/morphological changes, heat damage, glial inflammation, excitotoxicity, or asepsis has to be minimized (Polikov, Tresco, and Reichert 2005; Nimmerjahn, Kirchhoff, and Helmchen 2005; Xu et al. 2007). Ideally this means that no or minimally invasive surgery will be necessary. There are a couple of ways this can be achieved; the hub can influence neural cells from outside the skull, or the hubs can be downsized to a nanoscale that will allow them to cross the blood brain barrier. This could be assisted by molecules that have the capability of chaperoning the hub molecules through the blood brain barrier.

In addition, the system should be small enough so that individuals can have freedom of motion to continue with daily life while or after the system has been active. This puts a number of limitations on the BCI system, where it will have to be largely wireless and can not consist of a large and/or heavy receiver system or battery pack. This can potentially be achieved if the hubs are constructed on a nano scale or if they have a smart mechanism to receive energy from the body or its surroundings (e.g. kinetic, magnetic or light energy).

If an invasive installation is necessary it will be important that the system is build in such a way that it has optimal longevity, allowing for many years, and optimally, a lifetime of usability. This will be determined by how the device interacts with the immune system. An effective system will not activate an immune reaction from the body that might lead to rejection of the device. Optimally the device should maintain a high quality connection for the duration of its lifetime. Modules that are build outside of the body should be easy to replace.

A different solution for this problem allows for a temporary implant that will activate and ameliorate the neuropsychiatric symptoms for many years or even a lifetime. Such a system might induce targeted neurogenesis or local alterations in plasticity.

INTERFACES

There are a number different ways in which a neural interface can read and write to the brain. The most classic method enables scientists to measure and modulate the brain through electric changes. Throughout the history of neuroscience a great number of different forms of electric interfaces have developed. I will provide an overview of the latest techniques using these different forms of electric interfaces. A relatively novel method of neural interfacing is through optic methods. Modulation of the brain with optic methods has taken a flight since the development of optogenetics. Meanwhile optic measurements of brain activity have developed with the advancement of fluorescence. I will discuss the most promising methods through which they are being used. Finally, I will touch upon some other modes of modulation, like acoustic methods and through nanotechnology.

ELECTRIC INTERFACES

The seminal research of early neuroscientists demonstrated how electrodes were able, for the first time, to explore how perception and action was caused by neuronal signaling. Wilder Penfield demonstrated that the electrical stimulation of the exposed temporal cortex could lead to re-activation of experiences and memories as reported by the conscious patients (Penfield 1959). This was one of the first crude explorations of neural interfacing in human patients. The goals of these studies was to investigate the functional role of individual regions of the cortex. Hubel and Wiesel demonstrated that they could measure the receptive field of individuals cells by inserting a micro-electrode into the visual cortex (Hubel and Wiesel 1962). They moved away from evoked potentials, as measured with electrodes on the surface of the cortex, which usually has a resolution of up to 1 mm^2. Thus including a large cluster of neighboring neurons. The development of the tungsten micro-electrode allowed for a significant reduction in the size and rigidity of measuring electrodes, allowing for “single unit” measurements with a 0.5 µm tip (Hubel 1957).

In the following decades, despite technological developments, in essence these methods stayed the same and gave rise to a large variety of research studies where stimulating and recording electrodes were at the core of the applied methods (Cogan 2008). One widely used technique is electroencephalography (EEG). This method uses recording electrodes to measure voltage fluctuations from the surface of the skull. Although EEG has relatively high temporal resolution the method suffers from high levels of noise and signal averaging, as the signal is recorded from outside the skull. One measure of interest that can be effectively measured with EEG are frequency ranges of measured voltage fluctuations; delta (δ), theta (θ), alpha (α), beta (β), and gamma (γ). Scientists have been able to teach individuals to consciously make changes in these voltage fluctuations. This change was then recorded and interpreted by a connected computer and translated in order to move the computer cursor (Wolpaw and McFarland 2004). This method has been effectively used in individuals with locked-in syndrome, and has the potential to help these and other patients with communication, environmental control, locomotion and neuroprosthesis (Cogan 2008). Although the non-invasive nature of this method has clear advantages, the low temporal resolution - it often takes up to a second to modulate brain rhythms - can be a huge limitation (Thakor 2013). Despite this limitation this method is currently used commercially to help improve meditation practices (choosemuse.com; Figure 2). Although it is currently unclear if this application will have merit in the long term, it does indicate that individuals are becoming willing to consider these methods in daily use, which will be important for clinical applications, and the non-invasive nature will help with approval by regulatory bodies like the U.S. Food and Drug Administration (FDA).

Figure 2: Novel applications of non-invasive brain electrodes. Muse, the brain brain sensing headband is an example of a commercial application of low resolution EEG to help improve meditation practices (Images by choosemuse.com).

Other more invasive developments in this field includes the electrocorticogram (ECoG). In this technique recording electrodes are placed under the dura, leading to a greater proximity of the recording electrode to the brains surface and thus higher signal-to-noise ratio (Thakor 2013). It has higher spatial and temporal resolution compared to EEG. Novel developments in this field demonstrate the benefit of a flexible sub-dural neural implant, a so called electronic dura mater, is better able to modulate neural signals without causing tissue damage due to its flexible nature (Minev et al. 2015) (Figure 3). The electronic dura mater is capable of providing chemical and electrical stimulation in the spinal cord allowing for restored locomotion after a paralyzing injury (Minev et al. 2015). The goal of developing minimally invasive electrodes has further progressed through the innovation of syringe injectable microporous flexible mesh electrodes (Liu et al. 2015) (Figure 3). These sub-micrometer mesh electrodes are able to be injected into the brain and unfold locally to allow for a tight integration while causing little chronic immunoreactivity. This group was able to successfully inject this mesh into the hippocampus of a live rodent brain, and showed that there was no significant increase in glial fibrillary acidic protein (GFAP), which can be a measure of adverse response to the injection of a foreign material. Furthermore, the mesh integrated successfully with the local extracellular matrix, which included cells that stained positive for neuronal nuclear antigen (NeuN), demonstrating integration with adult neurons (Liu et al. 2015).

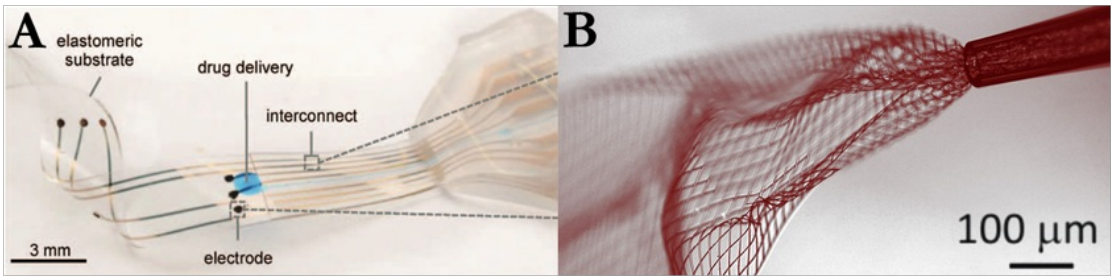

Figure 3: Developments in flexible electrodes. A. Electronic dura mater combines electrodes and chemotrodes in a silicone substrate (Minev *et al.*, 2015). B. Syringe injectable microporous flexible mesh electrodes (Liu *et al.*, 2015).

A different method of invasive electrode placement can be achieved with micro-electrodes. Micro-electrodes can measure single neurons, or when combined in a 2 or 3 dimensional array, can measure a population of neurons a few mm deep into the cortex. These micro-electrodes have a higher spatial and temporal resolution compared to ECoG, and are capable of measuring local field potential (LFP) and spike signals. Scientists have been able to use these micro-electrode arrays and closed feed-back loops to let a non-human primate use a prosthetic arm for self-feeding (Velliste et al. 2008). This field is now able to implant 4-8 3D micro-electrode arrays per primate, that can record extra-cellular activity of up to 500 cortical neurons per array (Schwarz et al. 2014). These implants have

demonstrated a significant longevity of up to 5 years, so far. Furthermore, this lab is now able to provide a wireless interface for the implant with relatively low power consumption that can support 128-channels for up to 30 hours uninterrupted up to a 3 meter range (Schwarz et al. 2014). This interface will allow for the observation and modulation of somewhat natural social interactions and behaviors.

This technology can further improve with the implementation of neurotrophic electrodes, these electrodes encourage growth into the hollow electrode tip using trophic factors, and thus greatly reduce the rejection rates and increase longevity (Kennedy et al. 2000; Kennedy 2012). Safety can be improved by significantly decreasing the size of the electrodes thought the implementation of nanotechnology. The energy issue can potentially be solved by implementing a novel technology that uses Wi-Fi to deliver power with a range of up to 6 meters (Talla et al. 2015). The downside is that the power provided reduces with a factor of 4 for each unit of distance you are further from the Wi-Fi source.

The methods described so far are using electrodes for recording neural signal. It should be noted these electrodes are technically capable of stimulating as well as recording neural signal, albeit not at the same time. It would necessitate changing the hardware connected to the electrode and doing so can reduce the quality of the recording capability of the electrode due to the change in impedance after reversal of the current. Thus these techniques are often developed and inserted separately.

Deep brain stimulation (DBS; Figure 4) is a method that uses electrodes for neural stimulation. It has been used for a variety of treatments that include; epilepsy, essential tremor, Parkinson disease, dystonia, Tourette syndrome, pain, depression and obsessive compulsive disorder (Perlmutter and Mink 2006). An application that more recently has become the focus of attention is DBS in treatment resistant depression (Mayberg et al. 2005). Despite the invasive nature and associated risks DBS has become a viable treatment option for severely treatment resistant depression. This is due to the relatively large group of individuals that do not respond to classic depression treatments and the severity of the disorder. Less than 40% of depressed patients achieve remission at the first treatment (McGrath et al. 2013), and up to 20% of patients entirely fail to respond to standard treatment options (Mayberg et al. 2005). Initial open label trials showed hopeful results, although unfortunately 2 recent multicenter, prospective, randomized trials failed to demonstrate efficacy and were discontinued (Morishita et al. 2014).

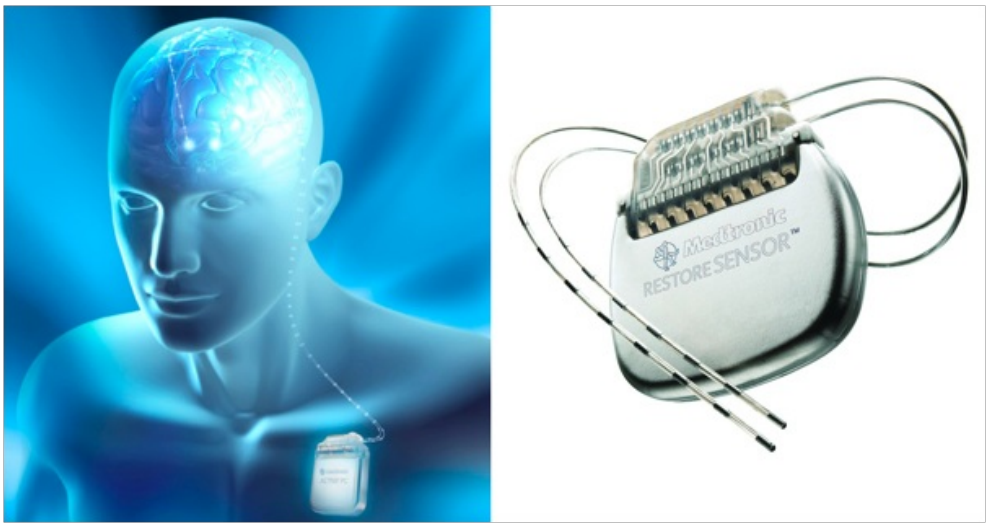

Figure 4: Deep brain neuro-stimulation. Example neuro-stimulator system used in deep brain stimulation for treatment of Parkinsons disease and treatment resistant depression. (Images by Medtronic)

OPTIC INTERFACES

Optogenetics is the genetic enhancement of neurons to become responsive to light. This is achieved through the production of light sensitive receptors that can either activate or inhibit neurons when light hits the enhanced receptor. There are a multitude of receptors (channels, pumps and G-protein coupled receptors) that selectively respond to light frequencies within their sensitive range. This allows for the real-time control of these genetically altered neuronal populations with millisecond precision (Fenno, Yizhar, and Deisseroth 2011; Bernstein and Boyden 2011; Deisseroth 2011; Tye and Deisseroth 2012; Goshen 2014). Channelrhodopsins (ChR) are cation channels that when illuminated with blue light lets in positive charge, thus depolarizing the cell (Bernstein and Boyden 2011; Tye and Deisseroth 2012). Halorhodopsins (NpHR) are inward chloride pumps that hyper-polarize the cell when illuminated with yellow light, thus inhibiting action potentials. Although these receptors often require tens of minutes to recover after illumination (Bernstein and Boyden 2011; Tye and Deisseroth 2012). A third group of light sensitive receptors are outward proton pumps, that hyper-polarize the cell. There are a number of different receptors available in this class that are all selective to different colors (Bernstein and Boyden 2011; Tye and Deisseroth 2012). Other engineered channelrhodopsins have ultra fast firing frequencies (>200Hz), or are opsin-receptor chimaeras with G-protein components allowing for intra-neuronal signaling cascades (OptoXR) (Tye and Deisseroth 2012). An interesting development has been the step function opsin (SFO), or stabilized step-function opsin (SSFO), allowing for a prolonged de-polarization of the target cell recreating a more naturalistic neural response (Tye and Deisseroth 2012).

The red light–sensitive optogenetic inhibitor cruxhalorhodopsin, or Jaws, as it was named after its shark based strain, enables the modulation of neural activity inside the brain. Red light is able to penetrate wider and deeper into the brain, thus allowing for a larger cluster of neurons to be activated, and the potential to shine the light from outside the dura, thus reducing the level of invasiveness (Chuong et al. 2014). An unwelcome side effect of extra-dural light is that it will only penetrate the brain to a certain extend, usually up to 3 mm deep, excluding the possibility to hyper-polarize cells deep in the limbic system (Chuong *et al.*, 2014).

An important advantage of optogenetics is that the molecule is encoded by a relatively small gene, allowing for the viral delivery in mammalian brains. This method enables scientist to select a promotor to express with the optogenetic code, thus driving greater expression of these receptors in specific cell types of interest (Bernstein and Boyden 2011). You can even do a combined expression of multiple opsins in one cell type, thus activating the cell with one color, and inhibiting that same cell type with a different color. Unfortunately, some cell specific promotors are quite long and will not fit in a viral vector, thus making this method unsuitable.

Technical progress has helped improve the hardware involved in optogenetic stimulation due to significant size reductions. This has lead to the ability to combine optogenetics with measuring electrodes; the optrode, which combines microscale, inorganic light-emitting diodes (μ-ILEDs) with multimodal sensors (McCall et al. 2013). The application of LED's instead of fiber optics allows for light to spatially distribute wider. This technique can then be combined with other ultra-thin multifunctional optoelectronic systems, like microelectrodes, microscale inorganic photo-detectors (μ-IPDs), and a temperature microsensor or microheater (Kim et al. 2013). This flexible system is attached to rigid structural support for injection (microneedle), that upon exposure to artificial cerebrospinal fluid will release from the optrode by dissolving the silk-based adhesive. As noted previously, neural tissue tolerates flexible devices better than rigid structures, leading to less inflammation. This device can then be attached to a wireless power module, based on radio-frequency scavenging (Kim et al. 2013). The sensitivity of this system can be improved by combining these devices into an array, or optrode multielectrode array (MEA)(Warden, Cardin, and Deisseroth 2014).

In addition to electrodes one can use optic methods to measure neural activity, a procedure that is based on fluorescence. Until recently cells would be loaded with a fluorescent dye that would activate upon calcium exposure. This method is invasive, toxic and is not cell type specific. With the development of genetically-encoded calcium indicators (GECI)(Lütcke et al. 2010), and genetically-

encoded voltage indicators (GEVI)(Gong, Li, and Schnitzer 2013) these issues have been largely resolved. These genetically encoded activity indicators enable fast-timescale readout of neural activity, nearly approaching the measurement of single action potentials (Warden, Cardin, and Deisseroth 2014). Furthermore, it allows for a bigger number of simultaneously recorded neurons, and it provides the possibility to record from single neurons for longer periods (Warden, Cardin, and Deisseroth 2014). The temporal and spatial resolution of the read out the fluorescent signal depends on the fluorescence imaging devices. There is great progress in this field, unfortunately currently most of these methods are not portable nor wireless (Grienberger and Konnerth 2012). A great example of the potential of these tools was demonstrated when researchers combined Jaws, GECI and two photon imaging to enable all-optical manipulation and recording of neural circuit activity with cellular resolution *in vivo* (Packer et al. 2014).

OTHER INTERFACES

An altogether different method to non-invasively modulate brain function uses ultrasound techniques. With the use of transcranial focused ultrasound scientists are able to target the cortex up to 18 mm deep (Legon et al. 2014). Although not a new technique its application in human neural modulation has only recently been explored. When transcranial focused ultrasound was applied to the human primary somatosensory cortex, results showed that it enhanced the discrimination abilities of the volunteers as compared to the sham condition (Legon et al. 2014). Pilot studies indicates that transcranial ultrasound can alter mood and pain perception for up to 40 minutes when applied to the prefrontal cortex (Hameroff et al. 2013). It is thought that focused ultrasound may locally inhibit neuron firing, potentially inhibiting the spread of cortical excitation in response to a stimulus.

A similarly non-invasive form of neuronal stimulation uses transcranial magnetic stimulation (TMS). At high frequencies this method can induce epileptic seizures. At lower frequencies of stimulation, around the 1 Hz range, repetitive TMS produces inhibitory changes in the excitability of the motor cortex that are relatively robust and long-lasting (Wassermann and Lisanby 2001). Possibly caused by changes in plasticity caused by long term potentiation (LTP) and depression (LTD). TMS has been applied in the treatment of major depression, and has shown limited positive results (Ridding and Rothwell 2007). Results are likely due to insufficient use of a blind control condition (Wassermann and Lisanby 2001). An entirely different use of TMS in concert with EEG, was used in human brain-to-brain communication (Grau et al. 2014). This method was used as a demonstration of internet-mediated conscious transmission of information between human brains, without intervention of motor or peripheral sensory systems. Although this was just a proof of concept, it opens up interesting possibilities.

Other more exploratory techniques utilize novel developments in nanotechnology. Neuro-nano-technology (NNT) is a fast emerging field that aims to develop novel nano-structures that can interface with the brain (Vidu et al. 2014). Since the size of nano-structures is in the same order of of magnitude as neural biomolecules this technology is particularly suited to be used for neural interfacing. An excellent example is the novel application of magnetic nanoparticles, a compound that was previously employed for use as a contrast agent in MRI scans and as a cell-destructive therapy in cancer treatment, due to its magnetic hyperthermia (Pankhurst et al. 2003). Now combined with viral vector induced heat-sensitive capsaicin receptor (TRPV1) expression, scientists have been able to develop fast magneto-thermal control of neural activity in vivo (Chen et al. 2015). The TRPV1 gene is a naturally occurring gene that is expressed in many parts of the body and neural system. The placement of this gene under specific neuronal promotors in the viral vector can be used to select what type of cells this receptor will be expressed in. The response latency is at similar temporal dynamics as neuronal firing, enabling near natural modulation of specific populations of neurons. These particles have the potential to be used for long periods in vivo as they have limited cytotoxicity and they remain intact for several months after injection. This method requires an external coil generating a magnetic field, this low radio-frequency magnetic field can penetrate into the body without substantial attenuation and thus enable signal delivery deep into the brain (Chen et al. 2015). Taken together this novel

method has great potential to alter neural modulation without long-term invasive implants.

Other examples are more experimental, e.g. carbon nanotubes that have the potential to function as a nanoscale electrode (Vidu et al. 2014). Or DNA to design nanoscale origami robots that are capable of performing bio computing, though dynamic interaction with each other (Amir et al. 2014). A different group designed artificial micro-motors that are able to deliver drugs to regions more effectively than through simple passive diffusion (Gao et al. 2015). Other similar methods have been able to provide ultrasound driven propulsion of nanowire motors and magnetically propelled artificial flagella (Wang et al. 2014; Mhanna et al. 2014).

Finally, it should be noted that there are a number of techniques that despite their utility in research are outside of the scope of this manuscript. These include functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and magnetoencephalography (MEG). All of these methods rely on heavy machinery and it seems unlikely that any of these techniques will become of a scale that would permit portability within a reasonable time scale, thus failing the criteria set beforehand.

Table 1: Overview of Interfaces & Criteria

Electric Interfaces:	**Read**	**Write**	**Temporal resolution**	**Spatial resolution**	**Safety**	**Mode of Activity**	**See references:**
Micro-electrode	✔	✘	~0.0001 s	~0.01 mm	✘	Electric	Hubel, 1957
Wireless micro-electrode array	✔	✘	~0.0001 s	~0.05 mm +	✘✘	Electric	Velliste et al., 2008; Schwartz et al., 2014
Electrocorticogram (ECoG)	✔	✘	~0.001 s	~1 mm	✘	Electric	Thakor, 2013
Flexible electrode mesh	✔	✘	~0.001 s	~0.1 mm +	✘	Electric	Minev et al., 2015; Liu et al., 2015
Electroencephalogram (EEG)	✔	✘	~0.005 s	~100 mm +	✔✔	Electric	Wolpaw & McFarland, 2004
Deep brain stimulation (DBS)	✘	✔	~0.01 s	~0.6 mm	✘	Electric	Perlmutter & Mink, 2006; Mayberg et al., 2005; Morishita et al., 2014
Optic Interfaces:	**Read**	**Write**	**Temporal resolution**	**Spatial resolution**	**Safety**	**Mode of Activity**	**See references:**
Optogenetics	✘	✔	~0.001 s +	~0.2 mm	✘✘	Optic	Fenno et al., 2011; Bernstein et al., 2011; Deisseroth, 2011; Tye & Deisseroth, 2012; Goshen, 2014
Jaws	✘	✔	~0.001 s	~0.2 mm +	✘	Optic	Chuong et al., 2014
Wireless Optrode	✔	✔	~0.001 s	~0.25 mm	✘	Optic, Electric	McCall et al., 2013; Kim et al., 2013
Multi-array silicon probes	✔	✔	~0.001 s	~0.25 mm	✘✘	Optic, Electric	Warden et al., 2014
Jaws, Genetically encoded Ca^{2+} indicators (GECI) & two-photon microscopy	✔	✔	~0.001 s	~0.2 mm +	✘✘	Optic	Packer at al., 2014
Other Interfaces:	**Read**	**Write**	**Temporal resolution**	**Spatial resolution**	**Safety**	**Mode of Activity**	**See references:**
Transcranial ultrasound	✘	✔	~ 0.02 s	~5 mm	✔✔	Acoustic	Legon et al., 2014; Hameroff et al., 2013
Transcranial magnetic stimulation (TMS)	✘	✔	~0.1 s	~10 mm	✔✔	Magnetic	Wasserman & Lisanby, 2001, Ridding & Rothwell, 2007, Grau et al., 2014
Neuro-nano-technology (NNT)	✘	✔	?	~0.00002 mm	✔	Electric, Magnetic, Acoustic	Vidu et al., 2014; Amir et al., 2014; Gao et al., 2015; Wang et al., 2014; Mhanna et al., 2014
Magnetic nanoparticles	✘	✔	~0.000002 s	~0.00002 mm	✘	Magnetic, Heat	Chen et al., 2015

Future Directions

Ultimately the question remains as to how best we can use these novel methods. Merely being able to read and write neural responses will not be sufficient to help treat psychopathology. A deeper understanding of the underlying brain circuits will be of major importance for the effective modulation of behavior and cognition. Although this will not come effortlessly: "*There are many populations of synapses to probe, and many types of plasticity that can occur, so answering this question will require the systematic investigation of various circuit connections, behavioral readouts, plasticity induction protocols, and time points for testing.*" – Kay Tye (Tye 2014). Recently important steps towards a better understanding of these processes have been made with the help of some of the described techniques. Tye and Deisseroth (Tye and Deisseroth 2012) describe how the combined use of optogenetic techniques with molecular, electrophysiological, pharmacological and imaging techniques, has increased our knowledge of the amygdala micro circuitry involved in fear and anxiety. Another group has made great strides in a better understanding of memory engrams by showing that selective optogenetic activation of ensembles of dentate gyrus neurons can activate memories, as demonstrated by altered behaviors (Liu, Ramirez, and Tonegawa 2014). They also showed that the valence associated with a memory can be reversed when the same population of dentate gyrus neurons is optogenetically activated in a different context, while this is not the case for basolateral amygdala neurons (Redondo et al. 2014). The implementation of BCI techniques to probe neural microcircuits has the potential to further increase our understanding of the brain. The progress in understanding will enable improved designs of BCI systems, such that each system developed can iterate and improve on previous designs. This will eventually lead to systems that will be able to provide sufficient sensitivity and precision to effectively modulate cognition and behavior.

Although many questions remain, these are studies that show important progress in our understanding of neural microcircuits with the potential to help neuropsychiatric illness by selectively modulating aspects of these neural systems. These methods are recently being implemented by scientists at the University of Southern California, where they are developing a multi-input, multi-output (MIMO) prosthetic for implementation in the human hippocampus to aid with memory functions (Song et al. 2015). Further progress in this field will hopefully be spurred onward by two recent large investments by the European Union (Human Brain Project) and the United States (BRAIN Initiative), that aim to develop a greater understanding of neural micro-systems.

The most effective method for BCI in the treatment of neuropsychiatric disease will depend on the underlying symptoms. In the case of mood and anxiety disorders some theories indicate that abnormalities in neurogenesis and plasticity may cause over generalization and be at the root of many common symptoms (Kheirbek et al. 2012). BCI systems may be able to intervene by inducing increased plasticity at cortical and subcortical sites. It is thought that many neuromodulators influence the system trough increased LTP/LTD, causing plasticity (Wassermann and Lisanby 2001; Hatsopoulos and Donoghue 2009). For example, research suggests that the long-term effects of optogenetics are due to alterations in calcium influx, which may lead to an intracellular cascades inducing plasticity changes (Goshen 2014). Other disorders (e.g. autism, schizophrenia, 22q11.2 deletion syndrome) may be caused by under- or over-connectivity, and are thus better aided by a distributed system like magnetic nanoparticles, that are able to amplify or dampen signals at a variety of locations. For this type of system it could be useful if each node is aware of its specific location, its up- and downstream pathways and local cell specific functions. Currently magnetic nano-particles get activated without discrimination, and would be unable to be selective in what clusters would get dampened or activated. To solve this, nodes can either be placed in particular regions of importance with cell specific promotors. In the future, as particles approach nano scale, they have the potential to passively distribute throughout the brain. After distribution the nodes would probe their environment and surrounding nodes to learn their relative location and feedback from downstream nodes learn how to optimally influence the system.

Despite the great potential of BCI aided treatments, it will remain limited in certain aspects, as

BCI assisted neural modulations might be unable to alter the underlying pathology of the neuropsychiatric disorder, e.g. post stroke, multiple sclerosis lesions, amyloid-β peptide and plaque buildup in Alzheimer's disease. It does however have the potential to alleviate symptoms by substituting or supplementing the affected modalities. With regard to the use of viral vectors in human populations, unfortunately prolonged viral vector expression has the potential to lead to toxicity (Tye 2014). In other clinical trials viral vector based gene treatments have led to detrimental immune responses and oncogenesis (Thomas, Ehrhardt, and Kay 2003). These side effects will need to be addressed before viral vector injections can be safely used in human populations. Recent developments have attempted to address many of these issues through the progress in less immunogenic vectors, through the development of non adenovirus vectors that are less inflammatory, like Epstein–Barr virus, foamy viruses, SV-40, α-viruses and negative-strand RNA viruses (Thomas, Ehrhardt, and Kay 2003). While oncogenesis can be countered by introducing suicide genes in the vector (Thomas, Ehrhardt, and Kay 2003).

The past decade has produced amazing developments in the techniques used in neurobiology, and the progress seems to be accelerating. An important driver of this progress has been the continued exponential growth of computation capacity, which has largely adhered to Moore's Law since the 1960's. This computational progress has additionally spurred materials science, where advanced computing has lead to more innovative material designs, leading to a "golden age" in material sciences (Markillie 2015). The developments in materials science has lead to new super strong composites, smart materials that can repair themselves, metamaterials that can respond to light and sound, and nanoscale materials (Markillie 2015). These new developments have already started to improve BCI designs, causing progress that is so fast that it is almost impossible to keep up with, as you will note as this article is quickly become outdated. It does however provide excitement for what the next decade will bring.

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