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Review

Implantable brain computer interface: Challenges to neurotechnology translation

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ABSTRACT

This article reviews three concepts related to implantable brain computer interface (BCI) devices being designed for human use: neural signal extraction primarily for motor commands, signal insertion to restore sensation, and technological challenges that remain. A significant body of literature has occurred over the past four decades regarding motor cortex signal extraction for upper extremity movement or computer interface. However, little is discussed regarding postural or ambulation command signaling. Auditory prosthesis research continues to represent the majority of literature on BCI signal insertion. Significant hurdles continue in the technological translation of BCI implants. These include developing a stable neural interface, significantly increasing signal processing capabilities, and methods of data transfer throughout the human body. The past few years, however, have provided extraordinary human examples of BCI implant potential. Despite technological hurdles, proof-of-concept animal and human studies provide significant encouragement that BCI implants may well find their way into mainstream medical practice in the foreseeable future.

Contents

Introduction

An exponential increase in articles has appeared in the past decade regarding neural interface technology and the use of microelectrodes and signal transduction technology (Fig. 1). The concept of interfacing with cortical architecture to both detect and introduce signaling into neural networks has rapidly evolved from basic animal work occurring not more than four decades ago (Fetz, 1969; Humphrey et al., 1970; Keefer et al., 2008). This review encompasses both directions of the brain computer interface (BCI): namely extraction of neural signaling and insertion of signals to neural structures in the cortex. Furthermore, the challenges to translating these concepts from past decades of animal studies to humans are also worthy of consideration when pondering future applications.

Although Penfield is credited with systematically mapping the physiological architecture of cortical function in humans (Feindel, 1982; Schott, 1993), his discoveries were built on previous animal work by Sherrington and Foerster (primates and non-primates), Fritzch and Hitzig (dogs) and Ferrier (primates) decades previously. Translation of similar discoveries in animals to humans relied upon

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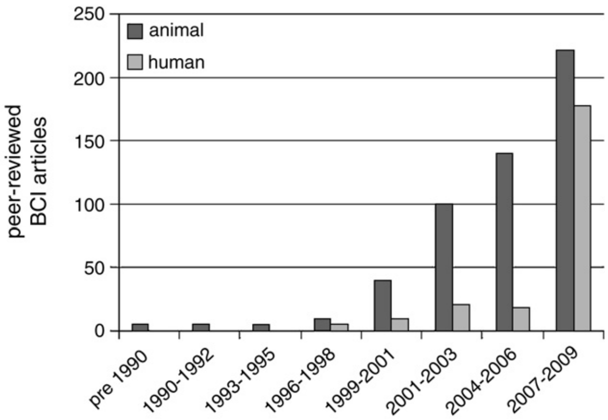

Fig. 1. Graph of BCI publications over time (modified from chart of peer-reviewed articles published from pre-1990 to 2006 (Kubler and Kotchoubey, 2007). A Medline search was performed for articles written between 2007 and 2009 using the search terms 'brain-machine interface,' 'brain–computer interface.'

appropriate technological breakthroughs enabling human recording and stimulation to occur. A similar rediscovery is now occurring with much more attention to detail, and opportunity exists for practical neural interfaces due to miniaturization of computer technology and more appropriately scaled electrodes that approach the level of neural signaling detail needed in potential applications. Yet, while these breakthroughs are being demonstrated frequently in the literature, there is a glaring lack of human data showing the application of such technology to disease specific problems. This review also serves to highlight the challenges of neuro-technology translation for the brain–computer interface.

The following discussion is organized into three areas that relate to clinical translation of BCI: use of BCI for extracting information for motor prosthetic control, use of BCI for delivery of signals to the brain, and the present extent of clinical trials for such devices.

Extracting commands from the brain

Physiological concepts in motor command coding

There are numerous reviews that have been published on the basis of neural coding of voluntary movement (Mountcastle, 1997; Reis et al., 2008; Schwartz et al., 2006). Details of the physiological and organizational basis of how cortical systems organize motor commands and other sensory phenomenon are pertinent when one considers developing interface technology to extract salient information for controlling motor prosthetics. There are some key concepts that emerge in the problem of acquiring motor control information from the brain.

The first important concept is that modules or units exist within cortical neuronal architecture that encode for movement direction rather than individual muscle contraction. Hence, details interpreting which muscles need to contract to execute a particular movement are not provided by these networks, merely the physical space where the movement needs to occur and the direction, velocity and force of the movement (a vector quantity). Georgopoulos et al. (1982) is frequently credited with the discovery that motor control by primary motor cortex neurons were preferentially "tuned" for movement in a particular direction, and that miniature loci of regional directional preference maps could be created for numerous muscle groups throughout the arm region of the primate brain. Similarly, others who studied eye movement and cortical organization in cats and primates agree that cortical modules exist that serve to tune the sensitivity of particular columns of cortical networks to particular directions of movement. This allows the cortex to "broker the information" of purpose rather than be concerned with the details of individual or pools of neuronal control. Such functions tend to be handled at the subcortical level (basal ganglia, brain stem, cerebellum or spinal cord level) and allow for significantly more efficiency of function (Middleton and Strick, 2000). Proof of the feasibility that such recordings can reflect intended movements in arm tasking in primates has been elegantly reported by members of Donoghue's group (Serruya et al., 2002), Schwartz's group (Schwartz, 2004; Taylor et al., 2002; Velliste et al., 2008), and Nicolelis' group (Nicolelis, 2001; Nicolelis and Ribeiro, 2006; Wessberg et al., 2000). In these experiments, primates were able to feed themselves with a prosthetic arm driven by a BCI connected to the primary motor cortex and connected to a robotic arm which allowed elbow flexion and extension and pincer grip open and close, enabling the monkey to manipulate objects and feed themselves. Presently, these robotic arms allow for grasping and retrieving objects and have allowed primates to feed themselves, while the primates were restrained from using their natural limbs. At best, these systems could allow up to four degrees of independent movement. Decoding these motor commands in these cases involved micro-electrode recordings from implanted arrays of 64–100 electrodes placed into the primary motor cortex (as well as non-motor regions) and optimized to detect neural signaling at layers 3–5 (1.5 mm depth).

In a separate laboratory effort, Donoghue et al. provided proof-of-concept of a BCI in humans for the first time in 2006 (Hochberg et al., 2006) whereby a patient with 3-year old, C4 spinal cord injury was able to control a "neural cursor" by thought (Fig. 2). This was the first human trial of an interface device (BrainGate system 100 electrode array containing 1 mm long electrodes in 4×4 mm; Cyberkinetics Neurotechnology Systems, Salt Lake, UT) that demonstrated a working detection system that allowed the patient to perform numerous voluntary virtual motor tasks via a signal processing system (Cyberkinetics Central Software). These tasks included spontaneous directed movements in which the patient would "drive a cursor" on a computer screen to various locations on the screen and select actions like "adjusting the volume, channel and power to his television" (Hochberg et al., 2006). Tracking movements and manipulating a robotic arm were also possible by the patient over weeks with reproducible detection, thereby demonstrating robustness and realtime processing capabilities with this system in a patient representative of a target population. The success of a BCI in a paralyzed patient, many years after a spinal cord injury, reinforces the idea that useful data can be extracted from chronically de-afferented and/or de-efferented conditions present with spinal cord or peripheral nerve trauma. Furthermore, these data provide evidence that cortical map reorganization in these patients may not hinder the use of a cortical based BCI implant.

Another feasibility study in humans was reported by Patil et al. (2004). This group from Duke reported the ability of humans to control gripping force strength with reasonable correlation (up to $R = 0.82$ coefficient) from micro-wire arrays temporarily implanted in thalamic and subthalamic regions. This study provides additional proof that a BCI interface can be developed for extracting motor control information in humans.

A second physiological concept important to the feasibility of a reliable, long term BCI is the degree of invasiveness for the neural interface to extract adequate information for control of motor prosthetics. There is clearly an exponential decay in the specificity of neural control signals for movement detection as an electrode is moved from intracortical, to epicortical (subdural array) to extracranial location (Fig. 3). Use of epicortical signal has been demonstrated in humans undergoing routine epilepsy monitoring with subdural grid electrodes (Schalk et al., 2008). In these patients, motor commands can be extracted from the electrocorticogram (ECoG) with adequate spatial precision to detect initiation of movement of the upper extremity and with reasonable directional accuracy. Although ECoG signals provide larger amplitude and reduced artifact

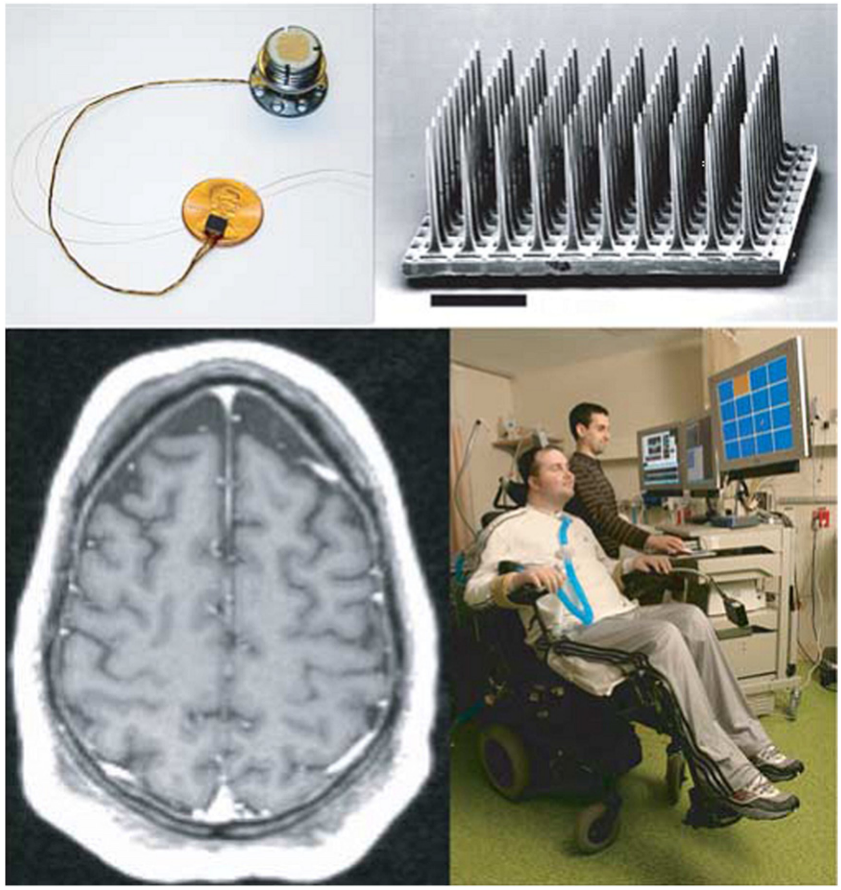

Fig. 2. First reported human BCI implant using the Cyberkinetics 100 micro-electrode array for recording movement related potentials in a high quadriplegic patient. Bar in upper right represents 1 mm length (modified from Fig. 1 of Hochberg et al., 2006).

signals, they contain information from a larger pool of neurons and therefore require more sophisticated signal processing for extraction of specific directional commands and spatial precision. And, although easier to obtain, these signals do not contain the specificity of single neuronal recordings. In light of this limitation, real-time signal processing of ECoG movement related neural signaling has become more feasible with improved processing speed and sophisticated algorithms. This advancement is allowing progress in the use of ECoG for BCI applications.

Implantable technology available today

The following components are needed to extract signals for a BCI system that could be used with a motor delivery system (Fig. 4). First, the electrode interface is defined as the electrical sensor that picks up the neural signals either through direct (intracortical) or indirect (epicortical) electrodes. Second, the amplifiers/analog filters are necessary to isolate the meaningful components of the signal and reduce unwanted noise. Third, the signal processing component processes the analog signal (usually in digital format) and packages

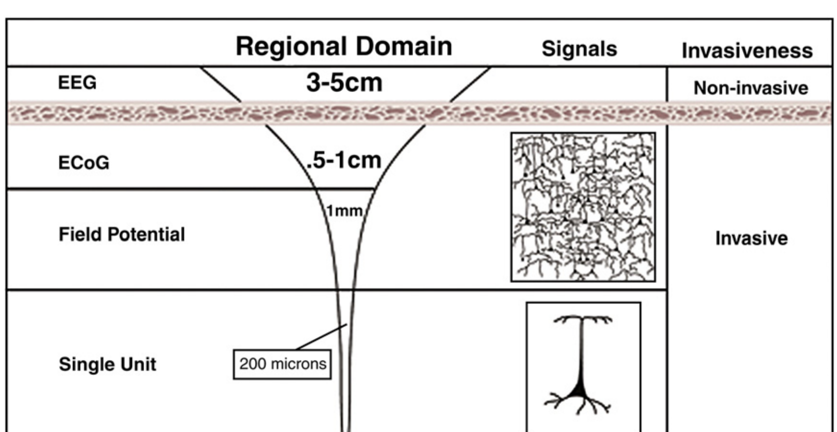

Fig. 3. Signal precision versus distance of electrode (reproduced with permission from Fig. 2 of Leudthart et al., 2006). Note that although increased precision and isolation of independent degrees of freedom occur with placement of electrodes intracortically, there is also a decrease in signal intensity and increase in noise, in addition to the increased risk of surgical access.

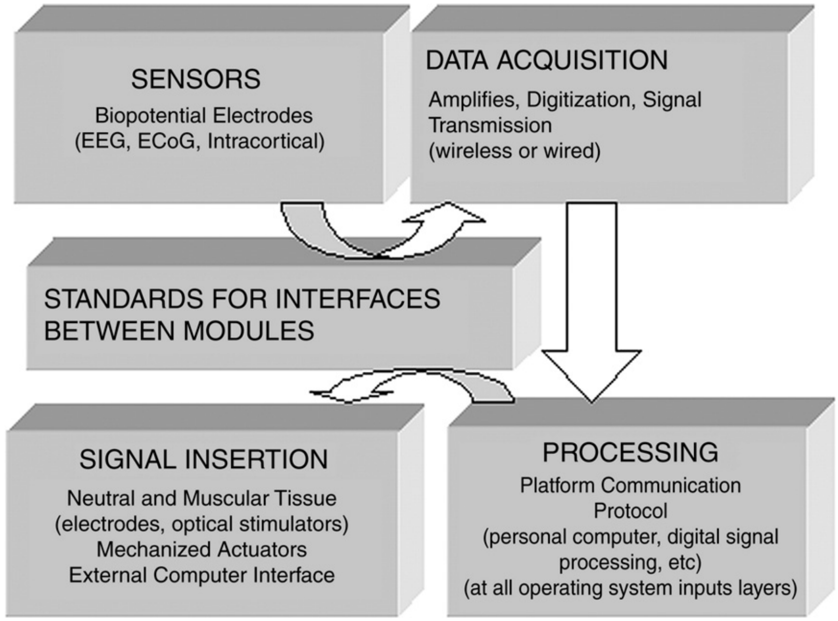

Fig. 4. Relationship and throughput of data extraction and data input with respect to BCI architecture. There are 4 key areas of throughput processing that have their own concerns regarding biocompatibility and technology. There are no standards in existence at present that delineates the interface protocol for high volumes of data transfer that will be required for BCI integration into the human body.

the output in a language understood by most computer processes (control signal). Fourth, there are significant technological concerns related also to the cabling or signal throughput from the previous three processes that deserve independent discussion.

The electrode–tissue interface has long been appreciated as the most important step in extracting robust, meaningful signals over long periods of time from neural tissue (Geddes, 1997; Pancrazio, 2008; Schwartz et al., 2006). It is one thing to demonstrate proof-of-concept in acquiring movement related control signals over a few days to weeks; it is a completely different task to continue high signal fidelity over months to years. With each new developed micro-electrode technology, issues regarding electrode fracture and signal drop-out needs to be addressed, and it is a common topic of discussion at neural interface workshops (Chen et al., 2007). More recent experience has provided examples of micro-electrodes in primates (Suner et al., 2005) and subdural electrodes in humans (Skarpaas and Morrell, 2009) that have functioned well for over 2 years in providing reliable command signals. Presently, these issues tend to plague micro-electrode recording electrodes more than macro-electrodes used for sub-dural or depth recordings of ECoG activity over long periods of time due to the difficulty in maintaining stable signals that retain spatial precision with micro-electrodes. Yet, new research challenges the adage that as electrodes become smaller, impedance (and consequently signal noise) rises exponentially. Research in the field of biomaterials and nano-technology has increased enormously in recent years to provide novel micro-electrodes that also have stable, low-impedance signals using non-metal polymers (He et al., 2006; Keefer et al., 2008; Pancrazio, 2008).

Amplification and filtration of analog signals acquired from neural electrodes has been approached either through circuits directly connected to micro-electrode arrays (Kipke et al., 2008) or cabling to the amplifier and processor located at a distance from the electrode (Donoghue et al., 2007). The value of proper signal conditioning increases significantly with reduction in electrode size, which consequently increases in electrode impedance and spatial precision. With newer developments in electrode surfacing, the need for analog signal conditioning may be significantly reduced for micro-electrode arrays.

Once signals are properly amplified and filtered, a significant range of opportunity exists for processing the desired signal components for use in controlling various output devices. Depending on how sophisticated the device is being driven by the BCI, signal processing can progress from simple, rapid translation of single movement related commands (controlling for instance, an on-off command signal to initiate single directional movement) to sophisticated command signals for controlling a large number of degrees of freedom (for instance, in a 21 degree of freedom artificial arm (Fite et al., 2006)). Both experiences in animals and humans with BCI demonstrate complex movements or control signals can be extracted with less than 100 channels; however multiple motor movements may be a completely different challenge. Signal processing networks that can process thousands or more data channels are presently undergoing development for BCI implants (Aghagolzadeh et al., 2008; Eldawlaty et al., 2008; Murray and Woodburn, 1997).

A fourth concern exists in the fidelity and transfer of data across distances. Some BCI designs prefer to locate the amplification and filtering circuitry on the electrodes themselves. However, others have transferred raw signals via cables to an amplifier and signal processor at a distance. Each concept has advantages and disadvantages. Placing the analog amplifier and filters on the electrode theoretically allows for improved signal-to-noise ratio and better fidelity when signals are processed at a distance from the electrode. The disadvantage is the need for delivery of power to the electrode array and larger bulk to a micro-electrode array. Cabling and signal transfer is a significant technological challenge when the number of channels of data increases and signals need to travel long distances. Impedance of electrical cables increases with distance and diminished size of fibers, in addition to being dependant on the conducting material (Geddes and Roeder, 2003; Liu et al., 2007).

Inserting signals into the brain

Physiological basis of sensory perception

Similar to the organization of motor modules in the cortex, the sensory region of the cortex also contains highly organized neural networks that are tuned to specific sensory modalities (Kaas and Collins, 2001). Although each sensory region of cortex has a preferential modality (e.g., somatosensory, visual, auditory cortex), it receives significant modulatory input from motor and associative regions, as well as inputs from other sensory regions of ipsilateral cortex through a rich arborization of unilateral association fibers. As a result, there are several important physiological concepts that are relevant to inserting natural or artificial sensation into the cortex through a BCI.

The first is that each cortical sensory unit is tuned to a physiological feature (e.g., visual perception of edge movement in primary visual cortex) for which perception is selected, rather than individual point sources of information. For example, it has been well studied that neurons in the primary visual cortex are tuned to movement of a visual object in a particular receptive field rather that recreating a one-to-one map of the retinal pattern on the visual cortex. Another example is found in primary somatosensory cortex (Brodman's area 3b, 1, 2), whereby different physiological features such as joint movement or fine touch are coded in adjacent areas for the same digit (Kaas and Collins, 2001). Providing appropriate electrical stimulation paradigms that mimic the natural perception of a particular modality of sensation has not been well described. In order to recreate meaningful sensory experiences either from artificial sensors or detection from living sensory nerves will require a much more detailed understanding of how this is coded physiologically. Such studies are tedious and difficult to perform in primates, and are debatable on their relevance to humans. Recent work in non-human primate digit mapping by Roe and Chen (2008) using fMRI techniques provide additional high-resolution insight into sensory coding and its potential use in BCI devices.

A second important physiological concept that has practical value for the BCI is the fact that multiple regions of the body provide input into each sensory module of the cortex. This can be used to retrain a particular sensory region to interpret one mode of sensory input as an indicator of another sensory modality. For instance, deafferented peripheral nerves in primates result in large-scale remapping of the entire throughput of adjacent topographic regions that now provide innervation to the cortex in an expanded receptive field (Florence and Kaas, 1995; Sadato et al., 2004). Activation of visual cortex by tactile stimulation is found in humans who are blind, as demonstrated by Sadato et al. (2004) using fMRI techniques, clearly demonstrating that the visual cortex has been “re-tuned” to respond to sensory stimuli.

Use of this physiological phenomenon is undergoing significant scrutiny for use in paralyzed patients. Danilov and Tyler (2005) have utilized the expanded sensory map of the tongue region of the brain to create an oral prosthesis that provides vibrotactile stimulation of the tongue in small distinct regions that reflect alternative sensory phenomenon, such as head tilt and truncal location with respect to gravity (postural signaling) in patients who are posturally impaired.

Implantable technology available today

Auditory restoration via the use of implantable stimulation devices has rapidly progressed over the past several decades. Arguably the application with the most extensive clinical impact to date is that of cochlear implants. These implants work via direct electrical stimulation of the sensory epithelium (basilar membrane) to treat neurosensory hearing loss. While the focus of this review is direct CNS interfacing of BCI implants, a few useful observations can be made from this peripheral interfacing application that may be generalizable to direct CNS BCI applications. First, cochlear implants have had the most success if the patient has already had some hearing during critical periods of development (Busby and Clark, 2000). To decode incoming signals reliably, it is easier if the brain is prewired to expect signals with certain kinds of statistical regularities. Second, though the sensory coding at the cochlea is relatively straightforward, there are still some aspects of normal hearing (e.g., musical appreciation or sound source separation) that are still elusive, possibly due to limited spatiotemporal resolution at the electrode interface or coding strategy of the filter (Leal et al., 2003). Strategies for overcoming these limitations are described above. Third, neural downstream targets of the interface show plasticity with changing inputs: post-implant sensory reorganization can occur (Eggermont, 2008). The advantage of this is that implant efficacy can be increased through postoperative behavioral training.

For an example of a direct CNS interface, the auditory brain-stem implant (ABI) is probably the best example of a BCI that has emerged with significant clinical impact on a group of patients with damage to the acoustic nerve requiring central nervous system input (Colletti et al., 2009; Schwartz et al., 2008). This has been available since 1993 and has continued to expand in channels and complexity of speech recognition software so that the present system employs 21 electrodes. Today, speech recognition is moderately acceptable at best and involves regular programming adjustments every few months for at least the first year post-implantation. In animal studies, improved dynamic range of tone perception and lower thresholds were noted when changing the implant from surface stimulation over the cochlear nucleus to a penetrating micro-electrode array. Careful review of these data should yield significant value when contemplating the trade-offs between surface versus penetrating electrode stimulation in other sensory modalities. Additional value appears to exist by placing the stimulating electrode more distal in the sensory circuit (inferior colliculus) with penetrating electrodes in both animal and humans studied to date (Lim et al., 2008).

A different story may evolve when reviewing the history of visual prosthesis. Retinal prosthetics have evolved over the last decade; however, resolution of visual images is poor at best with these devices. Unlike cochlear prosthetics which provide sensory input to the cranial nerve with better resolution than more centrally located implants, it appears that cortically based implants may have some advantages technologically over retinal prosthetics (Cohen, 2007). It appears that the larger spatial resolution of visual processing at the cortical level allows for easier electrode design and access to individual visual circuits. Yet, the level of visual processing at the cortex no longer represents a pixilated image raster but rather complex visual motion with directionally tuned preferences. The resulting images “seen” by a patient who underwent a surface, visual cortex implant (primary cortex V1) have generated a lot of enthusiasm in the literature for clinical benefit to blind patients (Dobelle, 2000; Dobelle and Mladejovsky, 1974). It appears that, like auditory prosthesis, penetrating, intra-cortical electrodes provide higher spatial resolution and potential for improved restoration of sensory perception.

Like auditory brain stem implants, another location for a visual BCI implant can be the lateral geniculate body (LGN) of the thalamus. Animal studies have shown that visual process occurs with significant spatial resolution in LGN (Kara et al., 2002). Consequently, Pezaris and others have explored the advantages of stimulation in LGN with micro-electrode arrays in primates and humans (Pezaris and Eskandar, 2009; Pezaris and Reid, 2009). The potential for meaningful vision (estimated at a minimum of 500 pixels/field) appears to be within reach in the next decade with this approach. Issues that need to be overcome involve the design of a practical electrode density needed to align stimulation with the highly organized and compact LGN architecture, as well as refinement of the physiological coding for creation of visual images. The disadvantage of LGN as a potential BCI target is the need to place a high density of electrodes deep within the brain and the risk of damage to critical adjacent structures the lie around the LGN.

Somatosensory prosthetics have yet to be implemented as the primary reason for implantation. However, there is much discussion in the recent literature regarding the role of closed-loop feedback systems for artificial limb control (Leuthardt et al., 2009; Leuthardt et al., 2004; Patil and Turner, 2008; Schwartz et al., 2006). Particular details regarding stimuli paradigms that create useful sensory perception in humans are largely lacking in the literature. The best example, in the literature, of somatosensory stimulation is the beneficial paresthesias produced in patients undergoing thalamic deep brain stimulation for pain (Kringelbach et al., 2007; Rasche et al., 2006). Although paresthesias are generally considered a side effect of brain stimulation for the treatment of pain or movement disorders, it is nonetheless an important clinical indicator of localization of stimulus efficacy. Patients who benefit from somatosensory stimulation typically have deafferentation pain (either centrally or less commonly peripherally), and it is assumed that stimulation of second or third order neurons in the somatosensory pathway restores some lost neural activity in these circuits. Paresthesias also can be produced with deep brain stimulation used for movement disorders; however, this form of sensation is usually short lived and perceived as a "side-effect" by the treating clinician. It typically arises from spread of the stimulus from a rather large electrode (1.5 mm long × 1.2 mm diameter contact) beyond the therapeutic zone (typically a concern with thalamic stimulation). The design of a therapeutic implant with smaller contact area may provide a more realistic zone of efficacy if one is considering thalamic or capsular targets for a somatosensory prosthetic. To date, we are not aware of implants specifically designed to reproduce various types of sensory modalities such as light touch, vibration, or pressure in the form of a BCI implant.

Clinical translational challenges

Human studies published to date

So far the availability of complete BCI systems available for clinical implantation are exemplified in the auditory prosthesis literature. Experience with multiple brain stem auditory implants that can be placed either at the junction of the cochlear nerve with the pons or in the lateral foramen of Luschka into the cochlear nucleus are examples of leading edge technology available to the commercial market (Schwartz et al., 2008). Visual cortical implants have been anecdotally reported by Dobelle (2000) as a complete BCI implant tested in a blind human but not available as a commercial product, and not reproduced by other centers.

A partial BCI component has been clinically tested in the arena of motor prosthetics by Donoghue's group (Donoghue et al., 2007; Hochberg et al., 2006), whereby a tetraplegic patient could control a robotic arm by thought. The sensing system, a 100 micro-electrode array on a 4 × 4 mm chip has been approved by the FDA for investigational use. However, this array (Cyberkinetics Neurotechnology Systems, Inc., Foxborough, MA) requires connection to an external processor through a transcutaneous connector secured to the skull. Human use is strictly investigational and not developed yet for complete implantation.

There are no commercially available products at all whose purpose is to provide somatosensory stimulation for restoration of tactile sensation in the head, body or limbs. We believe it would be useful to pursue in patients with limb amputation who would receive an artificial limb to achieve more realistic function through closed-loop integration.

Issues regarding BCI implants that need to be addressed

There a number of barriers that exist to the development of BCI devices before such implants become available to surgeons for implantation in patients. Some of these are physiological, some are technical, and some are commercial.

Physiological barriers to further development of the BCI interface include understanding spatial coding in sensory systems in particular. And even though motor cortex physiology has been nicely demonstrated for hand movement, there are minimal reports regarding efforts to decode walking and postural control from implanted electrodes. Furthermore, involuntary motor control has significant clinical impact and has not been discussed much in the literature other than in the context of spasticity management or pain related to spasticity and rigidity. Clinically, many patients complain about abnormal muscle tone and resting motor state more so than inability to initiate voluntary movement (Westgren and Levi, 1998). It is an anatomical fact that the majority of descending motor tracts represent involuntary commands, and therefore it would seem that effort should also be directed to understanding the role of such pathways in enabling neuroprosthetic control of muscle tone and involuntary coordination of movement between the actuated limb and other muscle groups. Adequate function of any BCI should include not only an objective assessment of the success of the bioengineering goals, but also assessment of quality of life improvement and evidence of improved neurological function. As BCI implants emerge in the clinical literature, parameters such as motor improvement, sensory discrimination, pain and mobility scores as well as quality of life scores and a sense of potential economic benefit to society should all be considered in the merits of BCI base therapy versus existing pharmacologic or other biotechnology therapy.

The same issues that need further development also apply to sensory BCI implants. Sensory prosthetics require significantly more understanding regarding temporal and spatial resolution resulting in more realistic sensory experience through a BCI. One significant deficit in providing more realistic sensory restoration is an understanding of the stimulus parameters that mimic natural signally among central sensory systems. In particular, when using electrical stimulation, pulse shape, duration, intensity and coding frequency do not closely match what is recorded clinically when micro-electrode recordings are analyzed in humans or animals. For example, spike frequency is often clustered in short bursts when analyzing single-unit potentials, but the BCI stimulation paradigms rarely mimic this complexity.

Technological hurdles are numerous in the design of stable, long-term BCI implants that are clinically viable. There are numerous lessons to be learned from auditory prosthesis regarding signal processing, stimulus coding and spatial distribution through implanted electrodes of auditory implants that span over a decade of clinical experience. The value of learning from this community upon the broader community of neuroprosthetics is exemplified in the merger of the auditory prosthesis community with the DBS and neuroprosthetics community through the NIH Neural Interfaces Workshop the past 5 years (Pancrazio, 2008; Rousche et al., 2008). A number of technological problems have been highlighted in recent years which has driven research funding to specific goal directed solutions. These focused research agendas should provide more usable solutions for clinical products in the next decade.

In particular, the debate regarding penetrating electrodes versus surface electrodes for more spatially precise detection or stimulation is extremely germane and significant tradeoffs exist in the clinical literature from examples of each. It is appealing to the design engineer that if issues of neural damage, signal-to-noise problems, large scale electrode signal processing are addressed with acceptable clinical risk, then smaller electrodes that are closer to individual neural structures is the answer. So far, even a 4 × 4 mm array of 100 electrodes has raised concern by investigators regarding clinical safety, namely risk of intracortical trauma, hemorrhage, or infection. Interestingly, these concerns are raised more frequently by research scientists rather than by clinicians. Based on the literature and discussions at neuroprosthetic conferences, it appears that a majority of the concern for risk is based on anatomical and histological changes associated with insertion of the BCI. Clinicians who are involved in present day neurological device implants weigh this risk in the context of clinical loss, and this may well be acceptable to the patient and clinician when considering BCI implants in patients who are already paralyzed or blind when considering the potential benefit of restoring lost function. These issues are addressed daily in clinical practice for many patients facing decisions regarding insertion of a DBS electrode or cochlear implant in the context of their disabilities. It is our experience that patients are willing and, in fact, desirous to consider such options in the hope of improving their quality of life when faced with significant disability. It is thus most important for clinical investigators engaged in early trials of these devices to have a reasonable and well informed perspective on the risk:benefit ratio so as to allow pivotal human studies in neuroprosthetics to move forward.

One new avenue of emerging technology that may solve a number of spatial resolution issues is through the use of micro-optical arrays. The use of low energy lasers for transient optical neural stimulation through fiber optic cables has been described in peripheral nerves by Wells et al. (2007a,b) Stimulation specificity less than 400 μm in diameter without electrical artifact has been shown to be effective in mapping fascicles in rat sciatic nerves with this technique. It remains to be seen whether this can also be applied to cortical stimulation.

Perhaps the one barrier to the advancement of BCI beyond the academic environment is the commercialization potential of such implants (Leuthardt et al., 2006; Patil and Turner, 2008). Despite these technological hurdles, proof-of-concept animal and human studies have provided significant encouragement that BCI implants may well find their way into mainstream medical practice in the foreseeable future.

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References

Aghagolzadeh, M., et al., 2008. Impact of compressed sensing of motor cortical activity on spike train decoding in Brain Machine Interfaces. Conf. Proc. IEEE Eng. Med. Biol. Soc. 2008, 5302–5305.

Busby, P.A., Clark, G.M., 2000. Electrode discrimination by early-deafened subjects using the cochlear limited multiple-electrode cochlear implant. Ear Hear. 21, 291–304.

Chen, D., et al., 2007. Advances in neural interfaces: report from the 2006 NIH Neural Interfaces Workshop. J. Neural. Eng. 4, S137–S142.

Cohen, E.D., 2007. Prosthetic interfaces with the visual system: biological issues. J. Neural. Eng. 4, R14–R31.

Colletti, V., et al., 2009. Progress in restoration of hearing with the auditory brainstem implant. Prog. Brain Res. 175, 333–345.

Danilov, Y., Tyler, M., 2005. Brainport: an alternative input to the brain. J. Integr. Neurosci. 4, 537–550.

Dobelle, W.H., 2000. Artificial vision for the blind by connecting a television camera to the visual cortex. ASAIO J. 46, 3–9.

Dobelle, W.H., Mladejovsky, M.G., 1974. Phosphenes produced by electrical stimulation of human occipital cortex, and their application to the development of a prosthesis for the blind. J. Physiol. 243, 553–576.

Donoghue, J.P., et al., 2007. Assistive technology and robotic control using motor cortex ensemble-based neural interface systems in humans with tetraplegia. J. Physiol. 579, 603–611.

Eggermont, J.J., 2008. The role of sound in adult and developmental auditory cortical plasticity. Ear Hear 29, 819–829.

Eldawlatly, S., et al., 2008. Identifying functional connectivity in large-scale neural ensemble recordings: a multiscale data mining approach. Neural Comput.

Feindel, W., 1982. The contributions of Wilder Penfield to the functional anatomy of the human brain. Hum. Neurobiol. 1, 231–234.

Fetz, E.E., 1969. Operant conditioning of cortical unit activity. Science 163, 955–958.

Fite, K.B., et al., 2006. Liquid-fueled actuation for an anthropomorphic upper extremity prosthesis. Conf. Proc. IEEE Eng. Med. Biol. Soc. 1, 5638–5642.

Florence, S.L., Kaas, J.H., 1995. Large-scale reorganization at multiple levels of the somatosensory pathway follows therapeutic amputation of the hand in monkeys. J. Neurosci. 15, 8083–8095.

Geddes, L.A., 1997. Historical evolution of circuit models for the electrode-electrolyte interface. Ann. Biomed. Eng. 25, 1–14.

Geddes, L.A., Roeder, R., 2003. Criteria for the selection of materials for implanted electrodes. Ann. Biomed. Eng. 31, 879–890.

Georgopoulos, A.P., et al., 1982. On the relations between the direction of two-dimensional arm movements and cell discharge in primate motor cortex. J. Neurosci. 2, 1527–1537.

He, W., et al., 2006. Nanoscale laminin coating modulates cortical scarring response around implanted silicon microelectrode arrays. J. Neural. Eng. 3, 316–326.

Hochberg, L.R., et al., 2006. Neuronal ensemble control of prosthetic devices by a human with tetraplegia. Nature 442, 164–171.

Humphrey, D.R., et al., 1970. Predicting measures of motor performance from multiple cortical spike trains. Science 170, 758–762.

Kaas, J.H., Collins, C.E., 2001. The organization of sensory cortex. Curr. Opin. Neurobiol. 11, 498–504.

Kara, P., et al., 2002. The spatial receptive field of thalamic inputs to single cortical simple cells revealed by the interaction of visual and electrical stimulation. Proc. Natl. Acad. Sci. U.S.A. 99, 16261–16266.

Keefer, E.W., et al., 2008. Carbon nanotube coating improves neuronal recordings. Nat. Nanotechnol. 3, 434–439.

Kipke, D.R., et al., 2008. Advanced neurotechnologies for chronic neural interfaces: new horizons and clinical opportunities. J. Neurosci. 28, 11830–11838.

Kringelbach, M.L., et al., 2007. Translational principles of deep brain stimulation. Nat. Rev. Neurosci. 8, 623–635.

Kubler, A., Kotchoubey, B., 2007. Brain–computer interfaces in the continuum of consciousness. Curr. Opin. Neurol. 20, 643–649.

Leal, M.C., et al., 2003. Music perception in adult cochlear implant recipients. Acta Otolaryngol. 123, 826–835.

Leuthardt, E.C., et al., 2004. A brain–computer interface using electrocorticographic signals in humans. J. Neural. Eng. 1, 63–71.

Leuthardt, E.C., et al., 2006. The emerging world of motor neuroprosthetics: a neurosurgical perspective. Neurosurgery 59, 1–14 discussion 1-14.

Leuthardt, E.C., et al., 2009. Microscale recording from human motor cortex: implications for minimally invasive electrocorticographic brain–computer interfaces. Neurosurg. Focus 27, E10.

Lim, H.H., et al., 2008. The auditory midbrain implant: effects of electrode location. Hear Res. 242, 74–85.

Liu, X., et al., 2007. Implantable stimulator failures: causes, outcomes, and solutions. Conf. Proc. IEEE Eng. Med. Biol. Soc. 2007, 5787–5790.

Middleton, F.A., Strick, P.L., 2000. Basal ganglia and cerebellar loops: motor and cognitive circuits. Brain Res. Brain Res. Rev. 31, 236–250.

Mountcastle, V.B., 1997. The columnar organization of the neocortex. Brain 120 (Pt 4), 701–722.

Murray, A.F., Woodburn, R., 1997. The prospects for analogue neural VLSI. Int. J. Neural Syst. 8, 559–579.

Nicolelis, M.A., 2001. Actions from thoughts. Nature 409, 403–407.

Nicolelis, M.A., Ribeiro, S., 2006. Seeking the neural code. Sci. Am. 295, 70–77.

Pancrazio, J.J., 2008. Neural interfaces at the nanoscale. Nanomed. 3, 823–830.

Patil, P.G., et al., 2004. Ensemble recordings of human subcortical neurons as a source of motor control signals for a brain–machine interface. Neurosurgery 55, 27–35 discussion 35-8.

Patil, P.G., Turner, D.A., 2008. The development of brain–machine interface neuroprosthetic devices. Neurotherapeutics 5, 137–146.

Pezaris, J.S., Eskandar, E.N., 2009. Getting signals into the brain: visual prosthetics through thalamic microstimulation. Neurosurg. Focus 27, E6.

Pezaris, J.S., Reid, R.C., 2009. Simulations of electrode placement for a thalamic visual prosthesis. IEEE Trans. Biomed. Eng. 56, 172–178.

Rasche, D., et al., 2006. Deep brain stimulation for the treatment of various chronic pain syndromes. Neurosurg. Focus 21, E8.

Reis, J., et al., 2008. Contribution of transcranial magnetic stimulation to the understanding of cortical mechanisms involved in motor control. J. Physiol. 586, 325–351.

Roe, A.W., Chen, L.M., 2008. High-resolution fMRI maps of cortical activation in nonhuman primates: correlation with intrinsic signal optical images. ILAR J. 49, 116–123.

Rousche, P., et al., 2008. Translational neural engineering: multiple perspectives on bringing benchtop research into the clinical domain. J. Neural. Eng. 5, P16–P20.

Sadato, N., et al., 2004. Tactile discrimination activates the visual cortex of the recently blind naive to Braille: a functional magnetic resonance imaging study in humans. Neurosci. Lett. 359, 49–52.

Schalk, G., et al., 2008. Two-dimensional movement control using electrocorticographic signals in humans. J. Neural. Eng. 5, 75–84.

Schott, G.D., 1993. Penfield's homunculus: a note on cerebral cartography. J. Neurol. Neurosurg. Psychiatry 56, 329–333.

Schwartz, A.B., 2004. Cortical neural prosthetics. Annu. Rev. Neurosci. 27, 487–507.

Schwartz, A.B., et al., 2006. Brain-controlled interfaces: movement restoration with neural prosthetics. Neuron 52, 205–220.

Schwartz, M.S., et al., 2008. Auditory brainstem implants. Neurotherapeutics 5, 128–136.

Serruya, M.D., et al., 2002. Instant neural control of a movement signal. Nature 416, 141–142.

Skarpaas, T.L., Morrell, M.J., 2009. Intracranial stimulation therapy for epilepsy. Neurotherapeutics 6, 238–243.

Suner, S., et al., 2005. Reliability of signals from a chronically implanted, silicon-based electrode array in non-human primate primary motor cortex. IEEE Trans. Neural Syst. Rehabil. Eng. 13, 524–541.

Taylor, D.M., et al., 2002. Direct cortical control of 3D neuroprosthetic devices. Science 296, 1829–1832.

Velliste, M., et al., 2008. Cortical control of a prosthetic arm for self-feeding. Nature 453, 1098–1101.

Wells, J., et al., 2007a. Biophysical mechanisms of transient optical stimulation of peripheral nerve. Biophys. J. 93, 2567–2580.

Wells, J., et al., 2007b. Pulsed laser versus electrical energy for peripheral nerve stimulation. J. Neurosci. Methods 163, 326–337.

Wessberg, J., et al., 2000. Real-time prediction of hand trajectory by ensembles of cortical neurons in primates. Nature 408, 361–365.

Westgren, N., Levi, R., 1998. Quality of life and traumatic spinal cord injury. Arch. Phys. Med. Rehabil. 79, 1433–1439.