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New Perspectives on Neuroengineering and Neurotechnologies: NSF-DFG Workshop Report

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Abstract- Goal: **To identify and overcome barriers to creating new neurotechnologies capable of restoring both motor and sensory function in individuals with neurological conditions.** ***Methods:*** **This report builds upon the outcomes of a joint workshop between the US National Science Foundation (NSF) and the German Research Foundation (DFG) on *New Perspectives in Neuroengineering and Neurotechnology* convened in Arlington, VA, November 13-14, 2014.** ***Results:*** **The participants identified key technological challenges for recording and manipulating neural activity, decoding and interpreting brain data in the presence of plasticity, and early considerations of ethical and social issues pertinent to the adoption of neurotechnologies.** ***Conclusions:*** **The envisaged progress in neuroengineering requires tightly integrated hardware and signal processing efforts, advances in understanding of physiological adaptations to closed-loop interactions with neural devices, and an open dialog with stakeholders and potential end-users of neurotechnology.** ***Significance:*** **The development of new neurotechnologies (e.g., bi-directional brain-computer interfaces) could significantly improve the quality of life of people living with the effects of brain or spinal cord injury, or other neurodegenerative diseases. Focused efforts aimed at overcoming the remaining barriers at the electrode tissue interface, developing implantable hardware with on-board computation, and refining stimulation methods to precisely activate neural tissue will advance both our understanding of brain function and our ability to treat currently intractable disorders of the nervous system.**

Index Terms- Brain-Computer Interface, Brain-Machine Interface, Computational Neuroscience, Neuroengineering, Neuroethics, Neurostimulation, Neuromodulation, Neurotechnology

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I. INTRODUCTION

Rapid advances in neuroscience, engineering, and computing are opening the door to radically new approaches to treating neurological and mental disorders and understanding brain function. These new approaches are based on the ability to record and stimulate neural activity with increasing precision. This precision is leading to the rapid expansion of neural interfaces, devices that interact with the nervous system to restore or enable sensory and/or motor function. Examples of successful neural interfaces include cochlear implants for the deaf [1], retinal implants for the blind [2] and devices for deep brain stimulation (DBS) for Parkinson's patients and individuals with essential tremor and other motor symptoms [3].

This report focuses on a type of neural interfaces termed brain-computer interfaces (BCIs; also known as brain-machine interfaces (BMIs)). We use the term BCIs to describe devices that interface directly with the brain via recording and/or stimulation hardware. The origins of BCIs can be traced back several decades to seminal experiments by Eberhard Fetz who used BCIs to study operant conditioning of single neurons in monkeys [4, 5] and Jose Delgado who pioneered neurostimulation techniques [6]. Shortly thereafter, Vidal proposed the idea of non-invasive BCIs based on electroencephalography (EEG) [7]. The past two decades have seen a tremendous surge in BCI research [8, 9].

BCIs are classified according to several factors including the degree of invasiveness, and whether the BCI only records from the brain, stimulates brain regions, or does both ("bi-directional" BCI). Invasive BCIs can record from neurons inside the brain, for example from the motor cortex using intracortical arrays of electrodes. Such BCIs have yielded the highest information transfer rates and the best decoding performance to date, allowing human subjects to, for example, control robotic arm-and-gripper systems for self-feeding under laboratory conditions [10-12]. Noninvasive BCIs based on techniques such as EEG for recording from the scalp have typically been used for controlling cursors or selecting items

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from a menu for communication purposes for completely paralyzed patients. Such methods have been used effectively by people with extreme cases of amyotrophic lateral sclerosis (ALS; also known as Lou Gehrig's disease). Advances in non-invasive BCIs were recently summarized in [13] and include control in up to three dimensions [14].

BCIs based on recording from the brain-surface using electrocorticography (ECoG) provide a middle-ground in achieving higher signal-to-noise ratio than EEG and therefore potentially higher accuracy in decoding; ECoG is typically used for epilepsy diagnosis [15], but also provides the opportunity for testing ECoG BCI techniques for controlling cursors [16], decoding individual finger movements [17], and studying plasticity in the brain [18]. Despite these advances in BCI research, there are few examples where BCIs have made it out of the laboratory to clinical devices for in-home use, following the landmark successes of the cochlear implant and deep brain stimulator.

Previous workshops on understanding brain function [19] and interfacing engineering with life sciences and medicine [20] have outlined ambitious plans of action in areas of brain imaging and implanted neural interfaces such as customized electronics, devices and models to influence and understand brain function, and alternative interfacing methods. The NSF-DFG workshop focused on the challenges preventing the successful development and translation of BCIs to clinically-relevant, ethically-justified, FDA-approved devices. In the following sections, we review these challenges as identified and discussed by speakers and participants at the workshop. We summarize the specific areas of research that could benefit from an increased effort and investment from international funding agencies in order to bring BCI research out of the laboratory and into the daily lives of individuals who can benefit from these neurotechnologies.

II. CHALLENGES IN RECORDING AND STIMULATION OF NEURAL ACTIVITY USING INVASIVE TECHNOLGIES

Despite the tremendous progress that has been made in microelectrode technology as well as in scientific and clinical applications of intracranial probes in the past years, implantable BCIs have not found their way into routine clinical and daily-use applications. To be useful on a long-term basis and worth the potential risks associated with implantation, implanted BCIs using electrodes placed on the brain surface and within the brain must record neural activity reliably and stimulate neural tissue safely over many years. The main challenges in achieving these goals are 1) controlling the electrode-tissue interface and 2) the long-term stability of the implanted hardware.

According to Fernandez et al. [21], stable intracortical microelectrodes have to meet four generally agreed-on requirements: 1) bio-safety: electrodes should not harm the brain tissue, 2) bio-stability: implanted parts of a BCI must be stable in the "hostile" biological environment, 3) bio-functionality: electrodes should perform their intended function, and 4) bio-tolerability: the electrode-array should have the ability to reside in the brain for long periods of time. All of these features are closely linked to the mechanical, electrochemical, biochemical and metabolic interactions of the hardware and biological materials at the electrode-tissue-interface. The functionality and longevity of intracranial probes, including both intracortical microelectrode arrays and ECoG electrode grids, are mostly affected by uncontrolled events at the material-tissue interface and by a mismatch between the properties of the biological and non-biological materials. Therefore, research efforts in materials science, production technologies as well as immunobiology are clearly justified.

Generally, after implantation, an ideal electrode array should establish a stable mechanical and electrical contact with the tissue and should not provoke any host response. When a probe with metallic contacts is implanted, however, two responses occur: an electrical double layer is set up at the metal/electrolyte interface and a foreign body response with an activation of molecular and cellular cascades is triggered in the adjacent tissue [22, 23]. In combination with the material and geometry of the electrode, the double-layer determines the charge injection capacity and the impedance of the contacts, which are generally thought to be most relevant to stimulation and sensing, respectively. In case of chronic stimulation, the electrochemistry at the interface, in conjunction with the charge transfer across the double-layer, may lead to corrosion, electrode delamination, and tissue irritation which lower the effect of stimulation. Both for recording with a high signal-to-noise ratio and stimulation at low voltage levels, novel polymer-based electrode materials are under development [24, 25] and warrant further investigation.

The consequence of the foreign-body response is the encapsulation of the probe by fibrous tissue. Intracortical microelectrodes can typically measure action potentials in the vicinity of cells which are located up to 100 µm from the site where the signal is recorded. The capsule due to foreign-body reaction increases the distance between the electrode surface and active neurons, which lowers the amplitude of the recorded signals. The encapsulation also insulates the electrode which increases the stimulation threshold [26]. Further research is needed to elucidate molecular and cellular pathways involved in the material-specific immune response of the host tissue. Also important is studying how to coat the surface of implants with appropriate biomaterials to obtain a well-controlled integration of the implant into the neural tissue [23].

In addition to the foreign body response, the tissue may be harmed from the insertion of the probes into the brain [21] and from micromotion in the brain or on the brain surface due to respiration and blood flow [27, 28]. Current intracortically implanted microelectrodes are rigid and bulky compared to the size of single neurons leading to a "mechanical mismatch" at the electrode-tissue interface. As a consequence, neuronal processes are damaged, or small vessels are ruptured. Eventually, inflammatory reactions occur and the lifetime of the interface and the ability to record or activate specific groups of neurons is limited to time periods between several

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months to a few years. Using ultrathin and flexible electrodes which match the mechanical properties of the neural tissue may allow conformal integration and help decrease neuronal damage and the inflammatory response [29].

Currently, many types of probes are used in acute, subacute, and chronic settings in animal experiments and clinical applications. Examples include microelectrode arrays with up to several hundred recording sites situated on multiple probe shanks implanted intracortically to record and extract millisecond-scale information from single neurons [28, 30-33], and macro-scale ECoG grids or strips used to record local field potentials from the cortical surface [16, 33, 34]. For the fabrication of these probes, MEMS-based technologies are used to ensure high-quality microscale manufacturing. Suboptimal electrode fabrication and instability of the encapsulation of the electrode shanks and connecting leads are the major causes of electrode hardware failures [35, 36].

Current commercially available multishank probes support 96 (Blackrock Microsystems), 128 (Atlas Neuroengineering) and 256 (NeuroNexus) channels for simultaneous recording. Multishank probes with up to 1000 recording sites [31, 33, 37] are under construction. However, for high-resolution spatiotemporal recording and stimulation at scales needed to precisely monitor and control neural circuit activity, new technological concepts for miniaturization, multi-channel stimulation, and data acquisition are required (Fig. 1).

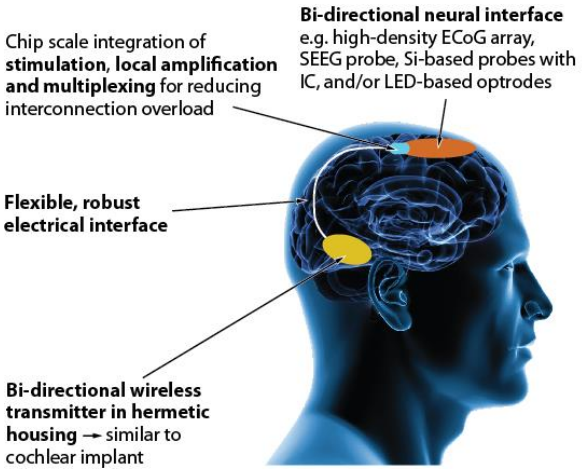

Fig. 1. Main challenges to be addressed to realize the next generation of BCIs (Image: Gunnar Grah, BrainLinks-BrainTools, using ©iStockphoto.com/angelhell and ©iStockphoto.com/Yakobchuk).

Simply increasing the number of probes for targeted stimulation and monitoring of neurons at many electrode sites in a small brain volume is inconsistent with the desire to minimize tissue damage. Optogenetic stimulation (see section VI) in combination with electrophysiological recordings [28, 38, 39], magnetothermal stimulation via previously injected nanoparticles [40], or the concept of "neural dust" with ultrasonic power and data transmission [41] may offer new ways to overcome the high-density multi-electrode dilemma. Despite research demonstrations using optically transparent windows in the skull and highly-controlled imaging conditions [42] , the current state of these technologies does not reveal that a non-invasive solution will be available in the near future for simultaneous, intracortical multisite stimulation, and multichannel high-density recording without the use of penetrating electrode probes.

III. CHALLENGES IN IMPLANABLE NEURAL INTERFACES

The main engineering challenges to be addressed in view of interfacing implanted electrode arrays with the outside world are 1) the electrical interconnections between the implanted array itself and either percutaneous connectors or implanted electronics for transcutaneous data transmission, 2) highly compact packaging solutions for the electronics with an appropriate number of electrical feedthroughs, and 3) a bi-directional, preferably wireless system for data transmission in a closed-loop implant. In addition, potential technical solutions have to fulfill the need for a high channel count, (i.e., more than 100 recording and stimulation sites), minimal system size, long-term stability for clinical applications, and large bandwidth for data transmission of rich neural signals at minimal power consumption by the electronics.

Neural probe arrays used for electrophysiological recordings necessitate appropriate interfaces to the extracorporeal instrumentation for data processing and data acquisition or closed-loop control. Example applications include neural prosthetics [43], epilepsy diagnostics [16, 44], functional electrical stimulation, cochlear [1] and retina implants [45], as well as dense arrays of micro optical light sources [46, 47] necessary for a location-specific optogenetic stimulation of neural tissue. In the case of BCIs aiming at restoring limb or full-body movements where 100,000 neurons may be needed [48], the need for a pronounced increase in channel count further extends the technical challenges in view of accommodating these interfaces in decidedly compact neural devices. Highly flexible and stretchable cables provide the requested mechanical robustness during the surgical procedure and body movements once the neural probe is implanted for directly interfacing the neural probes through either a percutaneously cabled connector or implanted electronics for transcutaneous data transmission. The cables are restricted, however, in the number of channels to be integrated. The same holds true for percutaneous connectors similar to those demonstrated in the clinical BCI trials performed with tetraplegic patients providing 96 contacts per device [43] or in clinical practice for focal epilepsy diagnostics using multiple stereoelectroencephalography (SEEG) probes with up to 18 electrodes per probe [15]. While this connector concept is tolerated in the case of epilepsy diagnostics due to its limited duration of intervention of typically less than two weeks, it must be circumvented in the case of chronic BCI implants in a clinical application where often strict space constraints have to be fulfilled.

Approaches to lower the interconnection overload of these interfaces, as illustrated in Fig. 2(a), may apply custom

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designed electronics for signal processing and multiplexing in order to reduce the number of output wires. This multiplexing approach is implemented by sequentially addressing single electrodes providing the full band-width of the recorded data [31, 49, 50] or by time-division analog multiplexing combining different signals onto a single output line [32]. The electronics might be directly integrated on the silicon-based probe arrays using complementary metal-oxide-semiconductor (CMOS) technologies (Fig. 2 b,c) [31, 32], integrated in a hybrid manner interfacing the polymer based electrode arrays [49-51] and silicon probe arrays [45, 52, 53], or packaged in a hermitic housing providing the interface to the electrode arrays [54]. In particular, the hybrid integration of electronic components requires additional technological efforts to minimize the interface size and thus achieve a pronounced increase in contact density. While both direct and hybrid integration could result in fairly compact system layouts by applying CMOS integrated circuitry and advanced MEMS-based assembly technologies, hermeticity is highly challenging in these cases. This barrier might be addressed using polymeric thin films [45] or chip-level packaging concepts [55]. In contrast, the integration of the electronics inside a hermetic housing as known from cardiac pacemakers currently provides the most advanced long term stability of these implants in the harsh body environment. Future key challenges in this context are highly compact housing dimensions for implantation in or on the cranial bone [56] or spinal vertebra, following perhaps examples from the retina [2]. Future devices, however, may need to accommodate up to several hundred electrical feedthroughs [54, 58], potentially in parallel with optical ports for data communication and optical/optogenetic stimulation. Obviously, an adequate robustness against mechanical impacts (e.g. hammer impact tests for cochlear implants according to ISO 45502-2-3) as well as a long term stability of 5, 10 or even 100 years [54, 58] are needed in the case of clinical applications. Further, the appropriate material choice for the miniaturized housings, such as stainless steel, ceramics and glass, have to comply with the requirements of bidirectional wireless data transfer and energy transmission either using RF signals or infrared radiation [59] . In view of clinical applications, an MRI safe/compatible system design is desirable for the housing, interfacing cables, and neural probes.

The bi-directional wireless module, with either a percutaneous connector or integrated in the implantable housing, must enable data processing of a large number of recording channels. The data might be transmitted to an external receiver as full spectrum neural signals multiplexed and digitized using implanted electronics (e.g., the implantable wireless device presented by Yin et al. [56] using 100 recording sites). The demand for hundreds or thousands of channels would, however, require the transmission of hundreds of Mbits/s of data, imposing a severe constraint for a wireless implant. Thus, the implanted recording system has to provide digital signal processing (DSP) with a robust decoding of neural signals enabling feature extraction, artefact removal and filtering such that only the relevant information from a large number of recording channels is being transmitted. Additionally, low power consumption is imperative for this implantable system to avoid tissue heating as well as maximize battery lifetime.

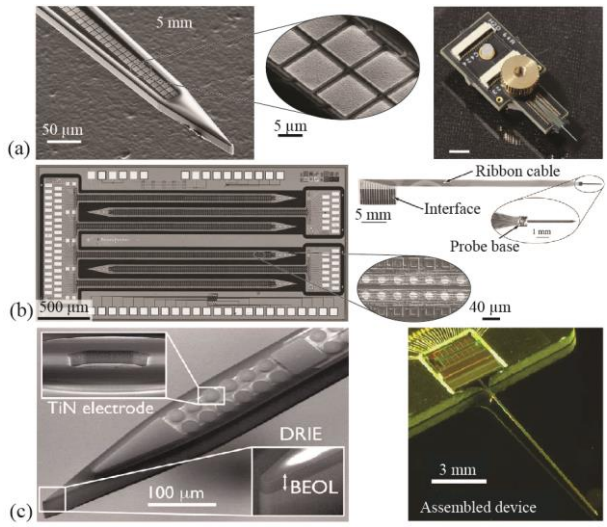

Fig. 2. Examples of passive and active high-density neural probe arrays; (a) passive probe with large probe base carrying one contact pad per recording site (adapted from Scholvin et al.[33]), and (b,c) CMOS integrated active probes with different levels of IC complexity to reduce the interconnection overload: (b) Integration of CMOS-based switch matrix into the probe shaft to simultaneously access 8 out of 188 recording sites, maintaining a small probe base (adapted from Seidl et al. [31]), and (c) integration of CMOS IC into the probe shaft and base to address 52 recording channels out of a total of 455 electrode sites (adapted from Lopez et al. [32]).

IV. CHALLENGES IN UNDERSTANDING AND DECODING BRAIN DATA

To build robust neural interfaces, it is imperative that we have a firm understanding of the computational principles underlying neural computation, plasticity, and coding of information in the brain. A prominent example of the importance of understanding neural coding and computation for brain-computer interfacing is the use of population coding methods for decoding motor intention to control a robotic arm [61-63]. These methods arose out of the seminal results by Georgopolous and colleagues on the population vector model of movement representation in the motor cortex of primates [64]. In this model, direction or velocity of movement is expressed as a linear combination of the preferred directions of motor cortical neurons weighted by their firing rates. Following this model, one can utilize a decoding strategy for neural control of a robotic arm in which a weighted sum of preferred directions of recorded neurons determines the direction of motion of the robotic arm. The utility of the population vector model has been demonstrated in examples of human subjects controlling a 10 degrees-of-freedom robotic

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arm-and-hand system for complex manipulation tasks such as picking and placing blocks [65]. Neurons used for control were found to be "multi-potent" in that each could represent multiple parameters of movement. Recalibrating the control mapping each day was found to yield the optimal performance.

A second example is extracting high-level goals, such as the end goal location of a reaching movement. Neurons in a region of the primate parietal cortex called the parietal reach region (PRR) respond selectively when the monkey reaches to a particular location in 3D space [66]. For BCI applications, this understanding of reach movements can be exploited to design an efficient strategy for goal-directed movement: rather than controlling a cursor or robotic arm moment-by-moment, one only needs to decode the final goal of the subject's intended movement, and then directly move the cursor or robotic arm end-effector to that location. Such a strategy [67, 68] has been demonstrated to yield the highest information-transfer-rates (ITRs) among different types of BCIs. Recording from parietal cortex may also convey information about bi-manual movements [69, 70] without the need to record from both hemispheres [71], as may be critical for BMIs to be used for persons recovering from stroke or other brain injuries [72].

Other work focuses on understanding signals from the cortical surface using electrocorticography (ECoG) and data reduction methods for neuroengineering. ECoG signals offer a semi-invasive alternative to intracortical recordings that penetrate the brain but come with the challenge of interpreting signals from the brain surface that reflect the activity of hundreds of thousands of neurons. It has been argued [73] that broadband spectral power, most clearly seen in a high-frequency band (70Hz and above) and also called the high gamma (HG) power, correlates well with the underlying population firing rate. Moreover, this high gamma activity is localized, compared to activity in lower frequency bands (e.g., "beta" or "mu" bands), making HG activity an especially useful feature for decoding fine-grained movements, e.g., individual finger movements [17]. Signals such as ECoG are recorded from grids of 64 or more electrodes. If one additionally utilizes multiple frequency bands for signals from each electrode, there is a need for reducing the dimensionality of the data before further processing. Traditional approaches such as PCA are useful for this purpose but ignore the dynamics of the underlying causes of the data. A new technique called Dynamic Mode Decomposition (DMD) overcomes this limitation by reducing the data to a dynamical system of coupled spatial-temporal modes [74].

Some of the remaining grand challenges in decoding brain data for bidirectional BCIs include utilizing knowledge gained from computational neuroscience to derive models (e.g., point process models) [76-79] and constraints to inform machine learning-based decoders, developing co-adaptive decoders that can cope with changing background brain states, developing methods for adaptively filtering undesirable components of brain signals, and providing sensory feedback via stimulation based on neuroscience-informed sensory coding models. More broadly, we have the major challenge of finding ways to control rich environments, devices, and software applications using limited and unreliable control signals.

The five-year perspective shared among most workshop participants was that robust brain-computer interfacing under non-stationary conditions can be reached by (1) further insights into the neurobiology of sensorimotor integration and decision-making, and (2) neuroscience-informed co-adaptive and unsupervised machine learning methods.

V. CHALLENGES IN BUILDING CO-ADAPTIVE BRAIN-COMPUTER INTERFACES

Traditional BCI systems collect data from a subject and then use this data to train a decoder or classifier that maps neural recordings to a control signal. However, brain signals change over time, both between sessions and within a single session, due to internal factors (e.g., adaptation, change in user strategy, fatigue) as well as external factors (e.g., changes in electrode impedance, difficulty in recording from the same neurons over extended periods of time). Thus, a decoder or classifier trained on data from a previous session may not be optimal for a new session due to the non-stationarity of the data. This makes it hard for the subject to learn to use the BCI and prevents its use in natural ecological environments. From a machine-learning perspective, the problem can be regarded as a *non-stationary learning* task where the system must continually adapt the function mapping inputs (brain signals) to outputs (control signals for devices). Such BCIs are called *co-adaptive BCIs* because the BCI and the user adapt simultaneously and cooperatively to achieve desired goals. Co-adaptive BCIs have been suggested as a remedy to the difficulty some users face in learning to control a BCI because with co-adaptive BCIs, the burden of learning control does not rest entirely with the user – the BCI can assist the user through co-adaptation [80-83].

One important prerequisite for building co-adaptive BCIs is understanding how the brain adapts when tasked with controlling an external device such as a cursor or robotic arm. Results from subjects using electrocorticographic (ECoG) BCIs to control a cursor suggest that for learning to control a BCI, the brain utilizes the same constellation of areas (premotor, prefrontal and posterior parietal areas) and the same underlying neural mechanisms as when learning a new motor skill [18]. Specifically, premotor, prefrontal and posterior parietal cortices exhibit decreased task-modulated activity as the users transition from a naive to a more experienced state (Fig. 3) [18]. Results such as these provide a neuroscience-informed foundation for building co-adaptive BCIs by monitoring a user's progress. They also highlight the challenge of developing computational models that allow us to gain a deeper understanding of neuroplasticity during BCI use [18, 85].

A simple strategy for making a BCI co-adaptive is to periodically update the decoder/classifier with newly collected data (for example, [86]). An important question that arises in this case is when and how often the decoder should be updated. One important strategy that has been explored is updating decoder parameters based on the performance of the decoder,

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wherein the decoder is re-trained whenever its performance falls below a pre-specified threshold [85].

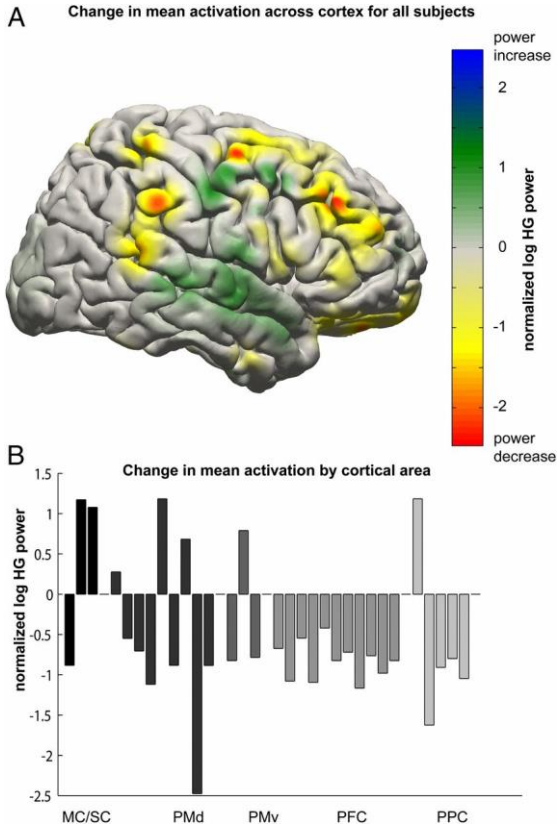

Fig. 3. Changes in Human Cortical Activity during BCI Learning: (A) Change in mean ECoG activation (in the 70-200Hz "high gamma" (HG) band) over 7 subjects from early to late trials in a BCI task. Subjects learned to control the vertical motion of a cursor moving from left to right to hit a target on the right side of the screen. Activations for individual electrodes were normalized against rest periods from the same electrode for a given run. Activation change values were blurred using a Gaussian filter to produce the image. Frontal areas and posterior parietal areas exhibited decreases in task-related activation over the course of BCI learning, similar to those observed during motor skill learning. (B) Change in mean activation across all electrodes, classified into approximate cortical areas. Specific cortical areas show significant change in mean activation from early to late trials. Figure from [18].

Methods for eliminating the initial offline calibration phase of traditional BCIs have been explored by several research groups, e.g., the Berlin BCI group [87]. These researchers propose an adaptation scheme for imagery-based BCIs that transitions from a subject-independent classifier operating on simple features to a subject-optimized classifier within one session while the user interacts with the system continuously. Supervised learning is used initially for co-adaptive learning, followed by unsupervised adaptation to track the drift of EEG features during the session.

Other researchers have explored the problem of continuous online adaptation of classifiers in a BCI. In [88], a mixture-of-Gaussians classifier was used to classify EEG patterns from 3 tasks: imagery of left- and right-hand movements, and mentally searching for words starting with the same letter. The feature vector consisted of the power for the frequencies in the range 8–30 Hz at 2-Hz resolution for 8 centroparietal locations and a gradient descent procedure was used to continuously adapt the parameters (mean and covariance) of the mixture-of-Gaussians classifier to achieve performance improvements of up to 20.3% for 3 subjects. A different approach to co-adaptive BCIs that is inspired by artificial intelligence techniques relies on the framework of partially observable Markov decision processes (POMDPs). In this approach, Bayesian inference is used to compute posterior probability distributions ('beliefs') over brain states, and BCI control actions are selected based on entire belief distributions so as to maximize total expected reward. Reinforcement learning is used to update the POMDP's reward function over time to achieve co-adaptive behavior. The results show that a POMDP BCI can automatically detect changes in the user's control strategy and co-adaptively switch control strategies on-the-fly [89, 90].

Grand challenges in the area of co-adaptive BCIs include achieving a deeper understanding of neuroprosthetic learning and control as a skill, designing BCIs with control protocols capable of handling competing tasks, developing methods for modeling and incorporating user learning and neuroprosthetic proficiency within the BCI control scheme, e.g., via adaptive features and intelligent control algorithms, and conducting longitudinal studies to investigate long-term efficacy of co-adaptive BCI algorithms.

VI. CHALLENGES IN MANIPULATIONG NEURAL ACTIVITY IN BI-DIRECTIONAL SYSTEMS VIA STIMULATION AND OPTOGENTICS

Creating a bi-directional interface requires that the CNS not only provides information via recorded activity, but that it also receives input in the form of artificial stimulation [91-93]. Such stimulation may provide sensory feedback directly to the brain, guide plasticity of neural circuits, or lead to movements of the limbs. To achieve these goals, artificial activation of the CNS requires techniques with specificity such as optical, magnetic or focused electrical stimulation. This section will review the state-of-the-art in these stimulation techniques, as well as their applications toward guiding neural plasticity, reanimating paralyzed limbs, and providing artificial sensory feedback directly to the brain.

Activity-dependent stimulation of the brain and spinal cord can lead to robust changes in connectivity within neural circuits [94-97]. Compared to a more general activation achieved by paired associative stimulation via transcranial magnetic stimulation (TMS; [98, 99]), activity-dependent stimulation effects are particularly long-lasting when applied within the CNS in a spike-timing dependent manner [94]. This

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suggests that specificity of both the triggering event and delivery of stimulation are important to produce robust changes in synaptic connectivity, likely via mechanisms of Hebbian plasticity [100]. The ability to produce precise, bi-directional plasticity [95] could be revolutionary in treating injuries and degenerative diseases of the CNS such as spinal cord injury, stroke, traumatic brain injury, and Alzheimer's disease. This potential for directing a selective 're-wiring' of the CNS motivates the need for advanced stimulation, in addition to activation of neural circuits to directly restore movement or sensation.

Brain computer interfaces can also be used to provide real-time control of electrical stimulation delivered to paralyzed muscles [101, 102]. Ongoing work has demonstrated that artificial stimulation alone can produce muscle contractions and lead to restoration of movement in the case of severe paralysis. Functional electrical stimulation applied to peripheral nerves and muscles can produce clinical benefits in gait and hand grasp function [103-106]. Stimulation applied within or near the spinal cord activates functional synergies, reflex circuits, and endogenous pattern generators that may simplify re-animation of paralyzed limbs while reducing fatigue associated with direct muscle stimulation [107-110]. Intraspinal microstimulation is capable of activating robust and specific forelimb and hindlimb synergies both before and after spinal cord injury [111-113], while epidural stimulation can enable volitional lower extremity movements even in the cases of clinically complete injury [114, 115]. Stimulation of the spinal cord is highly promising, and requires further development of devices that are flexible and robust to the mobility of the spinal cord relative to the bony vertebrae [116] that surround it.

Brain stimulation has the potential to produce artificial sensations and restore a sense of touch or proprioception to individuals who have lost these senses after injury. Animal and human subjects can perceive differences in electrical stimulation patterns applied to electrodes placed within or on the surface of the brain [117-120]. Although efforts are underway to locate and stimulate brain locations that naturally encode each sensory modality in a biomimetic fashion [121], there is also evidence that the brain can learn to interpret sensory information of unrelated areas via sensory substitution [122]. A challenge in restoring sensation is discovering the best manner in which to encode sensory information into artificial stimulation for optimal comprehension by the brain, especially for less-studied senses such as proprioception. In addition, alternative methods of stimulation should be explored given the challenges in specifically activating neural circuits using electrical stimulation explored below.

Electrical stimulation of the CNS is believed to activate a sphere of tissue around the electrode tip in proportion to the current delivered [123]. Complicating the specificity of electrical stimulation is the fact that axons and fibers of passage within this sphere are activated by stimulation at lower currents than neuron cell bodies [124, 125]. These axons synapse on local neurons with the benefit of natural trans-synaptic activation, or project great distances and diffuse the specificity of stimulation [126]. Although electrical stimulation of the CNS has a long history and several clinically useful examples including deep brain stimulation, cochlear and retinal implants, challenges in specificity of activation and natural recruitment of neural circuits motivates exploration of techniques such as optogenetics and magnetic stimulation.

Optical activation of neurons expressing light sensitive channels (opsins) demonstrates more localized and area specific recruitment of neurons compared to electrical stimulation (Ilka Diester; personal communication). These optogenetic approaches can also target specific cell types in transgenic animals or with targeted viral vectors. The development of novel opsins with both excitatory and inhibitory properties, and activated by different wavelengths of light provide the opportunity for bi-directional control of neuron circuits [127, 128]. Optical stimulation may also produce artifact free stimulation, an advantage for closed loop brain computer interfaces that aim to simultaneously record and stimulate neural activity. Challenges in this area include the development of flexible [129], multi-site [46, 47], multi-color optical stimulation hardware. Miniature LEDs are promising alternatives to rigid wave-guides leading to external light sources, but heat dissipation and electrical artifacts from local LEDs must be managed. Recent advances in wireless power delivery for other medical devices may lead to practical implantable systems for optical stimulation [130, 131].

Optogenetics shows great promise as a neuroscience research tool in animal models, and translation to human use is already underway. The most common method to deliver light sensitive proteins (opsins) to neural tissue is via viral transduction using the Adeno-Associated Virus (AAV). AAV is already being used in human trials for other gene therapy applications (e.g., [132]), reducing the remaining barriers to widespread optogenetic applications in human subjects to safety assurances when creating light-activated neural tissues. There are now ongoing trials in the United States and Europe using AAV-mediated optogenetics to treat blindness resulting from retinitis pigmentosa (e.g., clinical trial NCT02556736) and plans are underway to expand to optical cochlear implants [134].

Given the known tissue reaction to implanted electrical and optical devices [135], non-invasive methods of CNS stimulation also merit exploration if they can achieve specific activation of neural circuits for closed-loop BCI applications. A promising new method based on magnetic stimulation produces focal activation of neural tissue by creating resonance and thus local tissue heating via previously injected nanoparticles [40]. These nano-particles could potentially be targeted to cell-type or circuit specific locations using antibodies or similar methods. Modulated focused ultrasound is beginning to achieve activation volumes sufficiently small (currently about the size of a grain of rice) to be considered for focal CNS activation [136-138]. Given the extraordinary potential for CNS stimulation to guide plasticity, re-animate paralyzed limbs, and restore sensation, research efforts are clearly justified in advancing methods for robust, focal and

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minimally-invasive methods of brain and spinal cord stimulation for use in bi-directional BCI systems.

VII. CHALLENGES IN HUMAN BRAIN INTERFACES AND ASSISTIVE NEUROTECHNOLOGIES

Many of the fundamental advances in BCI have come from experiments in animals such as rodents and non-human primates. A major challenge is translating these results to humans – how will the techniques need to be modified and, what is the tradeoff between performance and invasiveness of different techniques for restoring function? Another challenge is in human neurostimulation. The most successful clinical human brain interface is the deep brain stimulator, currently being prescribed for reducing tremors and other symptoms of Parkinson's disease and other motor neurological disorders [3]. However, current implantable devices for neurostimulation, such as DBS devices, operate in open loop mode, causing a drain on battery power and more importantly, leaving the brain susceptible to side-effects. How can neurostimulation therapies be implemented using closed-loop implantable devices? A final challenge is developing human BCIs that can be used in conjunction with semi-autonomous robotic prostheses and other intelligent assistive devices – how can such BCIs leverage ideas and concepts pertaining to shared, semi-autonomous, and hierarchical control from robotics and control theory?

The most efficient path forward to human clinical trials appears to leverage existing and approved technologies (Utah array, ECoG) to permit expansion of human trials. For first-generation closed-loop systems, stimulation leveraging approved devices (DBS implants) are also permitting early human trials. On the other hand, newly developed devices promise substantial improvement over existing ones. Below we review progress and challenges on each of these fronts, as well as their combined application.

There is a broad and growing spectrum of brain disorders addressed by clinical research in neurotechnology. While the classical topics such as communication in severely paralyzed patients keep attracting great interest – and posing great challenges – disorders such as epilepsy, depression and stroke rehabilitation are attracting increasing attention [139-141]. Thus there is not a single translational goal of BCI technology, but many different applications, each with their own goals and constraints. For example, the optimal neurotechnological therapy in medial temporal lobe epilepsy will likely be not identical to that in other neocortical cases. In addition, BCI-based approaches for stroke rehabilitation in the acute phase will have different constraints and may leverage different mechanisms compared with rehabilitation in the chronic phase. Treatments for aphasia will differ compared to those for paralysis or neglect. We thus need to move beyond the idea of one-BCI-fits-all, and explore variations in systems and approaches. Nevertheless, common themes and challenges are evident across most if not all application scenarios.

To realize the different applications for clinical BCIs, we must establish a deeper understanding of the brain mechanisms involved in using and adapting to neurotechnology. For example, early BCIs succeeded with ALS patients having some residual movements but often did not translate to fully locked-in patients [142, 143]. This may be due to our lack of understanding about the exact pathophysiology unfolding during late stage ALS [144]. Beyond disease mechanisms, a need for a better mechanistic understanding also pertains to BCI operation, such as to the question of how the brain learns to control a BCI system on a network level. During learning to control an electrocorticographic (ECoG) BCI, wide-spread network-level effects of BCI training are observed [18], even extending to modulation of sleep spindle activity [145]. It may also be beneficial to understand and integrate non-cortical signals into existing decoding approaches to enhance robustness with respect to non-stationarity [146]. Finally, it may be beneficial to identify appropriate biomarkers for psychological conditions (such as Post-Traumatic Stress Disorder (PTSD)) in order to build bi-directional interfaces that can relieve the associated symptoms [147]

BCIs need to be tailored to real-life applications to gain practical importance. As a cautionary example, patients have abstained from using some advanced upper limb prosthetics because they are either too cumbersome, or do not provide a sufficient improvement in function to justify their adoption [148]. BCIs must be carefully designed to address patient-relevant problems that they can robustly solve in order to avoid a similar fate. Intelligent robotic systems in shared-control BCIs (e.g., [149-151] may help by reducing additional cognitive workload created by the interface and might thus increase the attractiveness of BCIs in out-of-the lab scenarios. Generally, there appears to be a tradeoff between invasiveness and information content in signals obtained from different recording techniques. Shared-control BCI systems are thus attractive, as they might increase performance without relying on more invasive recording techniques. Such systems, however, also pose specific challenges from the robotics perspective. For example tight interaction between the user and the robot needs to fulfill high safety standards, for which appropriate control methods and theoretical guarantees need to be developed and realized [153]. In addition, the robot needs to be able to accurately perceive the user and the relevant objects. Furthermore, innovative concepts for shared control interfaces, which allow the robot and interface to quickly adapt [150, 151] to changing capabilities for controlling the robot need to be developed.

VIII. CHALLENGES IN ETHICAL, LEGAL, AND SOCIAL CONSIDERATIONS

Among the most important challenges in neuroengineering and neurotechnologies are those pertaining to the ethical, legal, and social implications of human BCIs. Because we often take our brains to be the human organ with the closest ties to our identities and our senses of self [156], devices that alter our brain functioning – even with the aim of restoring or improving

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functioning – may be viewed as particularly worrisome or even threatening [156]. To be sure, many people already take pharmaceuticals (whether over the counter or by prescription) that affect their brain activity, and thus potentially influence their sense of self. Neural engineering devices promise more precise, targeted, real-time control, as well as the potential for hacking or other external interference. They are not fully unique in the ethical issues they raise, but they invite us to think carefully about traditional ethical issues in new contexts.

Even if BCIs can be made to function well with respect to their engineering aims - recording brain activity, identifying salient activity, translating data into relevant control signals, and stimulating appropriately - they still have to be acceptable to potential end-users, and provide a reasonable assurance with respect to issues such as safety, security, privacy, and respect for autonomy [157, 158]. In addition, attention should be paid to questions of access and issues of justice. We need to ask: What are the ethics of BCI research and communication of such research to the public and to potential research participants? When are BCIs ethically justified for use by human patient populations? When should we prioritize non-invasive BCIs over invasive BCIs, given different performance levels but also different levels of risk and commitment for the users? How might patient identity be shaped by BCI use? How much control should the individual user have over the neurostimulation parameters of a BCI? Who is liable when a co-adaptive BCI fails? What are the regulations that need to be in place? What are the ethical and social implications of non-medical BCIs for neural enhancement and augmentation?

A key issue in relation to communication has to do with managing public expectations and not over-promising on the functionality of BCI devices and systems [159]. Funding agencies may understandably look for transformative research, and researchers need to be able to promote their ideas by relaying a long-term vision of what they hope to achieve. The attractions of restoring movement, or assisting with brain-controlled prosthetics, communication devices, or wheelchairs, are significant given the potential for aiding individuals who have lost key functions and may not be able to operate existing devices on their own. Nonetheless, in order for the public to make responsible decisions about these technologies, they need to know how the devices will realistically work, now as well as in the hoped-for future. Limitations of the devices, as well as risks, must be clearly communicated alongside potential benefits and increased functionality [160, 161]. Helping the public to make informed decisions about the use of neurotechnologies will require promoting neuroliteracy as well as ensuring that researchers are transparent about the capabilities of their technologies [161].

Although BCI devices may rightfully be understood as simply another new tool for shaping the ways that humans interact with their environments [162], demonstrating the value of a new tool requires aligning it with the core values that members of the public hold. As an example, respect for autonomy has been a core value in medicine and bioethics, particularly in Western contexts. Individuals want devices that enhance their capacity for self-determination and allow them to choose according to their preferences and values. For some devices, though, even as they restore function in one arena (e.g., tremor control), they may undermine control in another (e.g., capacity for voice modulation) [163].

When their brains interact directly with closed-loop implantable devices, users may wonder about their own agency and responsibility for action [164]. Closed-loop bidirectional devices that appear to take the user even further "out of the loop" may thus be viewed with some skepticism by users, even though the devices are designed to save battery power and provide more targeted and user-specific stimulation. Of course, how we envision a closed-loop device's effect on autonomy may depend on the context and aim of the device. Some of these devices may be understood as effective treatments, quietly running in the background and allowing a person to be autonomous (as it might be in some therapeutic contexts, such as seizure detection [165]) ; others may present a potential constraint on a patient's sense of autonomy (as it might be with a closed-loop BCI designed to help the user generate movement), but perhaps with automation or safety constraints built in, so that the user may question whether she is fully the author of her movement [164]. Allowing an individual to choose when and how the device is operating – to have individual volitional control over the device, as opposed to needing a physician or researcher to intervene and control the settings - may be one way to ensure that BCIs do not threaten individual autonomy.

Still, individual control raises its own set of ethical issues, particularly when individuals may prefer settings that make them feel good but do not directly alleviate any medical symptoms [166]. Some scholars have noted that BCIs may be perceived as threatening to individuals' sense of personal identity and/or authenticity [167-169], while others argue that concerns about identity and authenticity are really more appropriately understood as worries about autonomy [170, 171]. Understanding how neural devices affect individual identity and/or autonomy and appropriately framing their role in enabling individuals to restore or maintain autonomy will be important ethical projects in this arena.

Although acknowledging and attending to public values is important for widespread acceptance of a new technology, sometimes dominant values may silence minority voices that raise important alternative views. As an example, consider the reaction of Deaf culturists to the prospect of cochlear implants. Cochlear implants were designed to offer deaf individuals a kind of hearing and thus a new form of access to the sensory world. They were heralded as a "cure" for deafness. But many Deaf culturists do not think of deafness as a condition that needs to be cured. Instead, they see it as a birthright to a unique way of life, and membership in a valuable linguistic and cultural minority group [172]. From this framework, cochlear implants were sometimes viewed as a tool for destroying a culture [156, 173]. Not all impairment groups have this same kind of attachment to their condition, of course, but understanding this minority perspective is salient for recognizing how threatening the introduction of a neural device can be. Rather than automatically thinking of deaf individuals

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as having a deficit that must be fixed, researchers might instead ask deaf individuals about how their functioning or flourishing could be improved.

Engaging likely end-users in the design of neural technology is not only pragmatic, but also morally significant, as it offers the opportunity to identify and acknowledge non-dominant perspectives on valuable forms of functioning. Engineers who aim to benefit others through design of devices surely should be aware of what those others want and what they see as beneficial. With respect to the development of BCI devices for mobility, for example, this might involve focus groups, interviews or surveys of people with spinal cord injury (SCI) or stroke to assess (a) their priorities for restoration of function, (b) the kinds of tradeoffs they might be willing to accept (in regard to privacy or security vs. increased independence), and (c) the design features they would prefer in order to adopt a technology (e.g., individual control over an "off" switch). Although many non-disabled researchers may presume that people with SCI have walking as a high priority, individuals more commonly point to concerns about urological or sexual functioning as their highest priorities [174]. Additionally, researchers might want to recognize how the offer of an experimental BCI device, even one that promises restoration of function, may threaten to disrupt one's hard-won identity as a disabled person.

A novel way for researchers to learn about public perceptions, end-user experiences, and values is to try to facilitate activities in which the two groups participate in a shared program. The concept of a café scientifique is one approach for such engagement, in which the scientists interact with the public through short presentations and discussions in cafés, pubs, or libraries in a face-to-face manner. This model depends on the researchers' capacities to present their work in accessible ways, and to be open to discussion. It does, however, still treat the researcher as the main expert.

A somewhat different approach brings together researchers and end-users to create a kind of art-form together. Because art allows opportunity for creative expression and may help us to understand what we think, and because both groups may be somewhat uncomfortable at the prospect of communicating through art forms, this kind of engagement puts the two groups on relatively equal footing: neither group can claim expertise in art, and yet each brings a different kind of expertise to the program. As an example, University of Freiberg's "BrainDance Days" invited neural engineers, Parkinson's patients, and clinicians to come together to dance under the guidance of professional choreographers, and to learn about how movement - and movement "disturbances" (*störung*) such as tremors – can be incorporated into creative expression and understood as raw material for dance (see https://braindanceenglish.wordpress.com/). In the process of creating the dance, scientific participants learned quite a bit about the experience of people with Parkinson's, and were able to appreciate their full human capacities rather than focusing on their deficits alone.

Developing new modes of engagement with the public and potential end-users of technology will be key to ensuring the development of ethically acceptable neural devices; doing so may require a variety of innovative strategies for informing the public, recognizing end-user areas of expertise, and helping scientists and engineers to acknowledge and be responsive to ethical and social concerns regarding neural technologies.

IX. CONCLUSION

A close collaboration of researchers in neuroscience, engineering, computation and ethics is required to produce reliable neural devices and brain computer interfaces that restore motor and sensory function to individuals with neurological disorders. Although many of the key components of a sensorimotor neuroprosthesis have been demonstrated, this report highlights important remaining challenges that will require focused efforts to overcome. One challenge is providing a stable electrode-tissue interface for long-term recording and stimulation. Promising approaches include flexible electrodes with very small features that do not induce a tissue response. A fully-implanted neural interface may be needed to reduce infection risk, but this introduces challenges in producing a reliable device with sufficient interconnects, computational power and data transmission bandwidth to interface with high-channel count neural probes. Other challenges include efficient on-board processing and decoding algorithms that co-adapt with the brain during operation of the device while obeying a strict heat-dissipation budget (1^{o}C for implants near the brain). Regulatory approval for these recording and stimulation devices will also be needed prior to human testing. Challenges in stimulation of neural tissue include providing naturalistic activation of neural circuits for restoration of sensation and motor function, as well as guiding neuroplasticity following injury for targeted rehabilitation. Emerging techniques using optical, magnetic, and ultrasonic stimulation may augment existing approaches based on electrical stimulation. Timely translation of brain-computer interfaces to clinical populations is needed to ensure that usability and added-function are practical in real-world settings. End-user perspectives and treatment priorities must be included throughout neurotechnology development. Finally, devices that interface directly with the brain must maintain the user's privacy, autonomy and sense of agency, while the associated ethical, social and legal issues of neurotechnology must be addressed proactively.

X. PARTICIPANTS

The following researchers participated in the NSF-DFG Workshop on *New Perspectives in Neuroengineering and Neurotechnology*, and contributed to the identification and discussion of the challenges summarized above:

Richard Andersen, California Institute of Technology; Polina Anikeeva, Massachusetts Institute of Technology; Tonio Ball, University of Freiburg; Falk Barz, University of Freiburg; Niels Birbaumer, University of Tuebingen; Benjamin Blankertz, Technische Universität Berlin; Ed Boyden,

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