IEEE
Advancing Technology for Humanity

IEEE brain

FUTURE NEURAL THERAPEUTICS

Technology Roadmap White Paper
Version 2

Identifying technology challenges and advancements required to promote development of next generation closed-loop neurotechnology

IEEE Brain
December 2020

The IEEE emblem is a trademark owned by the IEEE.

"IEEE", the IEEE logo, and other IEEE logos and titles (IEEE 802.11TM, IEEE P1785TM, IEEE P287TM, IEEE P1770TM, IEEE P149TM, IEEE 1720TM, etc.) are registered trademarks or service marks of The Institute of Electrical and Electronics Engineers, Incorporated. All other products, company names or other marks appearing on these sites are the trademarks of their respective owners. Nothing contained in these sites should be construed as granting, by implication, estoppel, or otherwise, any license or right to use any trademark displayed on these sites without prior written permission of IEEE or other trademark owners.

DOI: 10.23919/BRAIN.2020.00101

The mission of IEEE Brain is to facilitate cross-disciplinary collaboration and coordination to advance research, standardization, and development of technologies in neuroscience to help transform our understanding of the brain to treat diseases and to improve lives. Learn more about the program and activities at brain.ieee.org.

This white paper is offered as a tool to facilitate ongoing discussion in mapping future development of next generation closed-loop neurotechnology. As a living document, the information will evolve with input from key stakeholder groups over time. We welcome your feedback on this document and topic area. Please direct all comments and correspondence to: brain-clwp@ieee.org

Table of Contents

Background and Motivation 5
1. Introduction 6
1.1 Need for Roadmap....6
1.2 Roadmap Process....7
1.3 White Paper Structure 8
2. Scope and Timeline 8
3. Technology Stakeholders 9
3.1 Value Chain 9
3.2 Applications of Value Add for Stakeholders 12
3.3 Stakeholder Interactions....12
4. Neurotechnology Landscape....13
4.1 Definitions and Distinctions 13
4.1.1 Neuromodulation Technology 13
4.1.2 Neuroprostheses Technology....14
4.1.3 Brain-Machine Interface (BMI) Technology 15
4.2 Next Generation Closed-Loop Neurotechnology Development 16
4.3 Next Generation Closed-Loop Neurotechnology Applications 18
4.4 Applications by Industry 19
5. Design Drivers and Trends....20
6. Design Challenges 22
6.1 General Design Requirements 22
6.2 Technology Challenges 23
6.2.1 Scale 23
6.2.2 Materials 23
6.2.3 Electrodes and Sensors 23
6.2.4 Recording 24
6.2.5 Computation 24
6.2.6 Robustness 24
6.2.7 Power 24
6.2.8 Multiscale Signal Processing, Modeling, and Control....25
6.2.9 Communications 25
6.2.10 Safety and Reliability....25
6.2.11 Data Security and Privacy....26
6.2.12 Regulatory 26
6.2.13 Ethical....26
6.2.14 Translation 26
6.2.15 Usability....27
6.3 Additional System Challenges....27
6.3.1 Readout: Sensing, Biomarkers, and Feedback 27
6.3.2 Write In: Targets....27

6.3.3 Encoding/Decoding 28
6.3.4 Controller and Timescales 28
7. Technology Enablers and Solutions 29
7.1 Advanced Electrodes and Sensors 29
7.2 Improved Stimulation Technology 30
7.3 Improved Materials and Biocompatibility 30
7.4 Computation and Artificial Intelligence 30
7.5 Communication 30
8. Conclusions 31
9. Contributors 32
10. References 33

Background and Motivation

Over the last two decades, the neuroscience field has generated a tremendous amount of information on the cellular components of the nervous system. However, a major impediment to neurotechnology development has been the lack of a fundamental understanding of how the brain functions and how neural circuits operate. Early emphasis placed on the study of the brain through monitoring and recording single neural cells has yielded preliminary data, but an operational understanding of how the brain functions as a whole remains incomplete. In the United States, the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative[1] was formed to spur development of new tools and technologies required to deepen understanding of the brain, including efforts in high-throughput imaging approaches for mapping brain tissues. Other countries and regions around the world also have large-scale brain projects and programs to advance the field of neuroscience such as the Human Brain Project[2] and Brain/MINDS[3].

Multiple efforts are underway to record, to stimulate, and to better understand brain function fueled by interdisciplinary teams. One promising area of potential growth in neuroscience and neuroengineering includes developing new methods to both read and write activity into the nervous system through bidirectional closed-loop neurotechnologies.[4] Findings from these explorations may eventually lead to greater understanding of fundamental brain function as well as to a plausible theory of how the nervous system works. As such, we are at a moment of historical significance: the ability to read and write activity of the nervous system provides a crucial step in decoding and understanding the human brain.

Currently, a variety of neurotechnologies to treat movement disorders as well as neurological diseases are in the research and development phase, including closed-loop deep brain stimulation (DBS)[5]. Based on past technology trajectories, development of next generation closed-loop neurotechnologies that decode and encode neural activity from multiple nervous system sites (e.g., central nervous system, peripheral nervous system, autonomic nervous system [CNS/PNS/ANS]) will likely take place within the next 10 to 20 years. However, challenges to widespread adoption of such devices remain, and multiple technological challenges exist in developing these complex systems. Even so, the potential therapeutic benefits offered by closed-loop neurotechnologies will be essential in successfully addressing neurological disease and nervous system injury in the future as pharmacological therapies continue to exhibit limitations in efficacy.

It is therefore vital that at this time a path be articulated that lays out the projected trajectory of growth for closed-loop neurotechnologies as well as the necessary dependent technologies and advancements required to ensure success of next generation neurotechnology. Preparing a roadmap at the early stages will contribute to efforts to guide this development in an ethical and principled way, with the aim to benefit society as a whole.

1. Introduction

Research and development of closed-loop neurotechnologies has increased steadily over the last decade due in part to the potentialities that these technologies may offer for both the advancement of neuroscience as a field as well as for therapeutic interventions. Closed-loop neurotechnologies have shown promise for providing therapeutic and rehabilitative options[6] for patients, and offer potential for augmentative capabilities. These efforts range from restoring movement function after spinal cord injury (SCI), providing functional cures for neurological diseases such as epilepsy, and treating memory disorders such as Alzheimer's, to increasing learning speed and ability by selectively amplifying someone's plasticity or potential for plasticity, having the ability to transfer or recall memories, enabling control of robotic arms and exoskeletons, treating neuropsychiatric disorders, and creating devices that can both sense and stimulate activity in our sensorimotor system—changing the way our bodies interface with the world. Research employing closed-loop neurotechnologies for stimulating touch sensation[7], stroke rehabilitation[8], spinal cord injury rehabilitation[9], speech synthesis[10], and as a therapeutic alternative for treatment of Parkinson's disease[11] serve as examples of current and future pathways for exploration and translation.

Therefore, it is foreseeable in the near future that next generation closed-loop neurotechnologies will further improve the quality, rate, and scale of information transferred to and from the brain and nervous system structures, allowing for targeted and personalized therapeutic interventions and enabling intuitive and accurate control of external effectors. **The purpose of this white paper is to encourage community stakeholder dialogue on the challenges and advancements needed to develop these next generation closed-loop neurotechnologies.**[*]

1.1 Need for a Roadmap

IEEE occupies a unique position to provide guidance and recommendations in the field of neurotechnology as it continues its rapid growth cycle and maturation.[†] This roadmap process in part provides a model for thoughtful consideration of potential opportunities as well as the ethical[12] and social implications of neuroscience research for closed-loop systems and applications. Now is the time to explicate the questions and challenges surrounding the development of closed-loop systems as well as potential uses of such systems in order to identify and address problematic areas. The greater neuroscience community has a responsibility to think about these potentialities (both good and bad), as new technology will always bring disruption to society. Generating guidelines and possible solutions at this stage will benefit the field as a whole.

---

[*] *Open-loop neurotechnologies also have the potential to offer therapeutic solutions as well as add to knowledge of the brain and body systems. However, the purpose of this paper is to focus on next generation closed-loop devices that simultaneously read and write from and into the brain or other structures of the nervous system.*

[†] *IEEE recognizes that the future of neurotechnology is more than closed-loop systems and welcomes input on areas beyond closed-loop systems.*

Through collaboration with other stakeholders throughout the neuroscience community, IEEE can facilitate a technology roadmap that would define expectations of future closed-loop neurotechnology along with appropriate uses of that technology. Doing so will allow participants to realize critical benefits in areas such as:

- addressing needed changes to the regulatory arena and criteria for neurotechnology to assist with evaluation and approval of devices,
- facilitating professional and ethical frameworks and guidelines for development and responsible use of closed-loop technologies,
- identifying the necessary associated technologies needed to realize next generation closed-loop technology capabilities (e.g., improved sensors),
- optimizing investment strategies for research and development (R&D),
- leveraging R&D costs through resulting collaborations and partnerships, and
- providing valuable input on the formation of standards.

1.2 Roadmap Process

At this time, there is both a need and an opportunity to orchestrate a shared vision for future closed-loop neurotechnology.

The roadmap process begins with awareness and identification of the challenges, recognition of what factors are holding back the field, as well as gathering information on the new technologies that can be realized. A balance between vision and awareness that feeds into potential impact is required when determining successful technology solutions for the coming decade (e.g., treating Alzheimer's is clearly an opportunity to have high impact). The neuroscience community needs to think outside the box to consider promising solutions to therapeutic challenges, and the development of a technology roadmap is intended to serve as an aid for identifying scalable opportunities for the future.

With the support of The Kavli Foundation, IEEE Brain coordinated a Think Tank with shared stakeholders that took place in September 2018 with the goal of identifying future neurotherapies, including sensory, cognitive, and/or motor augmentation enabled by novel neurotechnology, as well as innovative experimental paradigms that harness the brain-body axis. Researchers from diverse fields including neurotechnology, systems and computational neuroscience, clinical practice, and neuroethics discussed potential pathways for growth of closed-loop control of neural systems in areas of mental health, bioelectronic medicine, and augmentation. In addition, an emphasis on neuroethics helped to identify and address key challenges beyond engineering and implementation.

Input from the September 2018 Think Tank was used in part to shape Version 1 of this white paper, published November 2019. The paper was shared with industry and government agency representatives, as well as researchers and business insiders, for feedback and comments. Input

received from stakeholders, along with updated technical information from this rapidly expanding field, forms the basis for Version 2 of this white paper.

The overall aim is to continue to build partnerships and collaborations among all stakeholders and mediate an industry-wide dialogue on development of next generation neurotechnology. The process begins with the development of this white paper, which identifies key technology domains. The goal is to have these technology domains help formulate roadmap working groups that would serve to further explore key drivers and challenges in order to update the paper on an annual basis. Development of a technology roadmap will require the support of many individuals engaged in roadmap working groups and discussions. IEEE Brain will work closely with the IEEE Roadmap User Group (IRUG) and the Steering Committee of the IEEE Roadmap Strategy and Governance (IRSG) Ad Hoc Committee to develop a plan and timeline for the roadmap effort.

1.3 White Paper Structure

This white paper presents the case for a roadmap effort for emerging closed-loop neurotechnologies. It is structured as follows:

- Section 2 covers the scope and timeline.
- Section 3 describes various stakeholders.
- Section 4 focuses on the state of the technology and presents potential use cases.
- Section 5 discusses design drivers.
- Section 6 highlights key challenges.
- Section 7 addresses potential technology solutions.
- Section 8 offers concluding statements.

2. Scope and Timeline

The primary goal of this white paper is to stimulate dialogue among community stakeholders on the challenges inherent in advancing to next generation closed-loop neurotechnologies and systems. These discussions will also assist with identification of the roadmap scope, along with a working plan to establish a comprehensive interactive IEEE roadmap.

Short-term plans consist of engaging with the wider neuroscience and neuroengineering community through workshops and the publication and distribution of the white paper in order to solicit input and begin to identify a consortium of stakeholders interested in championing this effort. Mid-term plans are to track development of related technologies as well as relevant neuroscience and closed-loop neurotechnology breakthroughs that could impact the ecosystem in the next 10 to 20 years, and update the working document every 12–24 months.

This IEEE Brain Technology Roadmap effort focuses on identifying technical and research needs for the future development of closed-loop neurotechnologies that access the nervous system. The translation of the white paper and roadmap findings is left to individual research institutions and industry entities.

3. Technology Stakeholders

There are several groups of stakeholders that will participate in or will be affected by emerging closed-loop neurotechnologies. These include:

- healthcare ecosystem (clinicians, patients, administrators, policy makers, caretakers, end users);
- neuroscience and biomedical researchers;
- academic institutions and science foundations;
- neuroethicists;
- the device and software industry (biomedical engineers, systems engineers, component manufacturers, developers);
- pharmaceutical companies;
- government entities and funding agencies such as the National Institutes of Health (NIH), National Science Foundation (NSF), Defense Advanced Research Projects Agency (DARPA), Office of Naval Research (ONR), Army Research Office (ARO), and Veteran Affairs Office of Research and Development (ORD);
- national labs including Sandia National Laboratory and Lawrence Livermore (LLNL);
- standards and regulatory bodies such as the IEEE Standards Association (IEEE SA) and the Food and Drug Administration (FDA); and
- tech companies and consumers in the entertainment/gaming/wellness ecosystems.

New stakeholders are continually emerging as neurotechnologies find new applications. Identifying emerging stakeholders is one aspect of this effort and every attempt will be made to be representative of all perspectives.

3.1 Value Chain

Different stakeholders define the added value for each group, which may differ according to needs and desires.

• Researchers/Developers—The desire to balance neuroscientific knowledge (e.g., how the brain functions) with a potential solution for a clinical need (e.g., epilepsy, mobility restoration) is often a driving force for research and development. Viability of translating a device or system to market is an inhibitor; profitability and competition with pharmaceutical solutions increase the need for value add of the proposed closed-loop system.

• Academic Institutions and Science Foundations—Investment in scientific understanding is often value-add for non-profit science institutions and academic research centers. Moving beyond lab research to translation is a driver for many institutions, but viable pathways to funding and profitable translation remain hurdles.

• Device Industry—Research, development, and manufacture of closed-loop neurotechnology devices is considered a potential high-growth area, but current high costs and regulatory constraints limit investment (including venture capital). Closed-loop therapeutic devices will need to become simpler and easier for clinicians to implement and patients to use in order to compete with pharmaceutical solutions. Direct-to-consumer devices will need to navigate efficacy and reproducibility hurdles for translation as well as acknowledge ethical challenges. Issues of payment via reimbursement from government agencies, insurance providers, and/or consumer out-of-pocket expense present challenges for neurotechnology in tandem with attaining provider-approved status.

• Component Manufacturers—Development of smaller, stretchable, low-power electrodes and sensors that are viable long-term is key to next generation devices. Multiple efforts in this area are underway (e.g., microwire and microthread electrodes, small carbon fiber electrodes, soft electrodes, optical sensors, tissue-engineered nerve scaffolds). Solutions to encapsulation and other biological incompatibilities will need to be overcome, offering devices that are both biocompatible and infection-inhibiting. Lack of standardization of materials and testing procedures (e.g., ageing, *in vitro* testing, and chronic *in vivo* testing), as well as miniaturization, remain significant challenges. Chronic *in vivo* testing of novel electrodes and sensors has been lacking compared to bench-top and *in vitro* testing, yet is critical for translation of these technologies for use in people.

• Computational Software Developers—Software and software interfaces need to be user-friendly such that clinicians, caretakers, and users are able to adjust settings as needed. Control algorithms for closed-loop neurotechnologies may take many forms, including traditional control systems engineering approaches, or the use of machine learning. For example, algorithms are needed to decode neural activity, control an external device such as a prosthetic limb or the stimulation amplitude for electrical stimulation of a paralyzed limb, as well as to encode sensory information back to the user. Machine learning in particular will be an invaluable component for next generation closed-loop devices. Development of advanced, adaptable algorithms and new ways to interpret and manage large data captures are needed to enable solutions that encompass the body's nervous systems while respecting and adhering to security and privacy issues.

• Healthcare Providers / Clinicians—Clinician input is crucial early in the development process for successful translation to clinical deployment. Ease of use, minimal risk during implantation procedures, and proven success as a therapeutic solution for difficult to treat conditions (e.g., movement disorders as well as neurological diseases) and/or those conditions that do not respond well to medication will be essential for adoption. Ultimately, less invasive or non-invasive approaches may be required to supplant pharmaceutical use; invasive devices will

need to further ensure precision efficacy to provide value add, as well as offer means for testing and repair of devices once implanted. Devices also will need to become embedded into the clinical practice plan, and ultimately serve as viable first option therapeutic solutions, rather than becoming viable only after pharmacological failure.

• Healthcare Insurance Providers—Cost of device may need to be less than pharmaceutical interventions over successful long-term use; however, value add and benefit to patient should be leveraged as the primary strategies for supporting neurotechnologies in the spectrum of health care.

• Users / Patients—Focus should be on the unmet needs of the patient/consumer and how the neurotechnology solves the problem, with user-centered (patient-centric) design employed early in the process. Users typically desire cosmesis, flexibility, and some control over as well as understanding of the device and its mechanisms. Cost and access will always be primary concerns for therapeutic devices. Concerns about privacy and safety (e.g., anonymity, hackability) as well as protocols for defining/labeling found biomarkers for social behaviors will need to be addressed. Sensitivity and specificity will be essential if the biomarkers predict maladaptive/criminal tendencies. Device lifespan and longevity (e.g., smart and changeable over time to supply upgrades to users) is of key importance to research subjects as well as end users, and also ties to concerns regarding clinical trial entry, trial cessation, and trial interruption. Researchers and manufacturers need to plan for long-term care of devices and have protocols and standards in place for trial and therapeutic use. For example, cochlear implants have a long history of use in people over decades. While it is uncommon to remove and replace cochlear implant electrode arrays, manufacturers have upgraded the devices to include improved sound processors.[13]

• Pharmaceutical Companies—Closed-loop neurotechnology devices are in many instances direct competition for pharmaceuticals. However, in cases where drugs have reached therapeutic limitations or for neurological or movement disorders that do not benefit from drug therapy, pharmaceutical companies may view closed-loop devices as an investment for co-therapy with pharmaceuticals for certain conditions.

• Government Entities and Funding Agencies—Government entities (including the NIH) provide the majority of research funding but are often result-focused, which may limit ability to take risks in development. Funding agencies should move to provide support for the broader spectrum of neurotechnology development from discovery through translation. There is a significant percentage of government funding that comes through defense agency channels, and much of this investment is predicated on developing closed-loop neurological systems and tools that increase defense advantage, accelerate learning and productivity, restore function and promote enhancement, and have the potential to work in partnership with artificial intelligence (AI). Potential tension between desires for augmentative applications vs. therapeutic solutions may require further emphasis on neuroethics.

• Regulatory Bodies—Regulatory bodies have historically been ill-equipped in their ability to evaluate closed-loop therapeutic devices, due in part to the predominance of pharmaceutical and/or external device solutions as well as lack of knowledge regarding the brain and nervous system as well as technology. Some progress has been made recently in altering regulatory focus (e.g., reclassifying BMI devices used for paralysis treatment and adapting approval requirements for non-clinical testing[14]). Further education and industry efforts may be needed to adjust requirements for clinical trials and approval for the range of closed-loop neurotechnologies, as well as monitoring the safety and security of approved devices.

• Standards—Currently, there is not a 'gold standard' requirement for materials and validation. Standardization protocols for components as well as closed-loop devices could offer a value add to the field as a whole. Ethical standards for development, testing, and implementation of devices are also required, as well as standards for privacy and security.

3.2 Applications of Value Add for Stakeholders

Next generation closed-loop neurotechnologies hold promise as therapeutic devices as well as fulfilling potential consumer applications. As of yet, not all stakeholder areas are determined. However, general traits required for stakeholders to recognize that a next generation closed-loop system is a value add in a particular therapeutic or consumer area likely would include at minimum:

- Increased efficiency and efficacy (dynamic stimulation based on feedback will better achieve desired outcomes/performance),
- Safety at all points and steps as well as cybersecurity of data,
- Device design grounded in real physiology,
- Neural targets would need to become more location-specific and precise,
- Individuality/customization available for each patient or user, and
- Autonomy/reduced cognitive load for clinician and for user.

3.3 Stakeholder Interactions

The roadmap effort will include a series of meetings over the course of several years with the aim to bring representatives and stakeholders together to assess relevant research and evaluate current technology and industry trends, projecting and mapping that information into future scenarios for emerging next generation closed-loop neurotechnology.

4. Neurotechnology Landscape

4.1 Definitions and Distinctions

For the purposes of this paper, *neurotechnology* broadly refers to any device using neural interfaces to read and/or write information from and/or into the nervous system. Neurotechnologies can be invasive or non-invasive and can target the central nervous system (CNS), the peripheral nervous system (PNS), or the autonomic nervous system (ANS). An example of an invasive, peripheral neurotechnology is a vagus nerve stimulation device that uses an intraneural nerve electrode, while a common non-invasive interface is electroencephalography (EEG). Neurotechnologies may include **neuromodulation technologies**, **neuroprostheses**, and **brain-machine interfaces (BMIs)** (Figure 1).

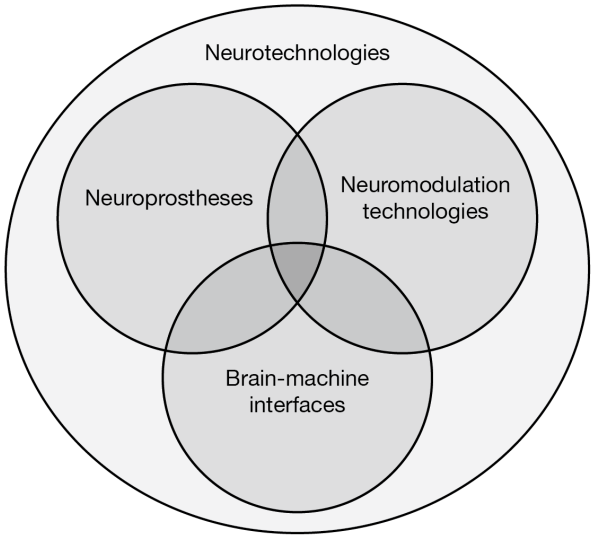

Figure 1. Venn diagram of neurotechnologies.

4.1.1 Neuromodulation Technology

Neuromodulation technology is the general term used to refer to any device that uses neural interfaces to stimulate peripheral, central, or autonomic nervous system (PNS, CNS, ANS) structures to modulate ongoing neural activity. Neuromodulation technologies can be either open-loop or closed-loop: open-loop technologies deliver a predefined stimulation pattern and lack feedback; closed-loop technologies use control signals or biomarkers (measurable signals associated with a specific physiological or pathological state) to control the delivered stimulation pattern or timing. Open-loop deep brain stimulation (DBS) or spinal cord stimulation (SCS) are two of the most common neuromodulation technologies.

Arguably, the most prominent and successful applications of closed-loop neurostimulation technologies are neuromodulation therapies for alleviating symptoms of neurological disorders,

including Parkinson's disease, where movement sensors are used to detect tremors and modify stimulation parameters, and for improving rehabilitation after stroke or spinal cord injury.[15]

Neuromodulation technologies that use volitional brain signals (or biomarkers consisting of brain signals that users can learn to regulate with the help of neurofeedback) in order to control the stimulation pattern might also be referred to as bidirectional BMIs. Applications for this technology potentially include neural rehabilitation for movement disorders as well as functional cures for neural abnormalities such as those associated with epilepsy or mood disorders; BMIs that decode user intentions to walk in order to precisely deliver spinal cord stimulation patterns that can facilitate locomotion[16]; and systems for closed-loop control of DBS for movement disorders.[17, 18] Multiple biomarkers have been pinpointed as possibly useful for modulation of the stimulation output for DBS, including features present in electromyography (EMG), EEG, ECoG, local field potentials (LFPs), and action potentials (APs). Control algorithms also can monitor the current level of activity compared to a baseline, and deliver stimulation as needed rather than stimulating continuously.

Other bidirectional neuromodulation neurotechnologies consist of employing optogenetics for neural stimulation, as in the CANDO (Controlling Abnormal Network Dynamics using Optogenetics) project currently in development for patients with focal epilepsy.[19] Here, the device provides precisely timed stimulation by continuously monitoring brain waves with implanted electrodes and modifying the waves through implanted light sources in order to modulate abnormal activity and prevent seizure development.

Finally, another example of a recent neuromodulation technology is the implanted responsive neurostimulator device—RNS System—from NeuroPace used for treating epilepsy. The RNS system is a responsive (closed-loop) focal cortical stimulator approved by the FDA for therapeutic use for medically intractable partial onset seizures in adults.[20] The closed-loop neurostimulator device continually senses brain activity through electrocorticography (ECoG) electrodes placed on the surface of the brain; when the device detects specific ECoG patterns, it delivers brief stimulation pulses in response and the stimulation in turn mediates the seizure-related activity that the device is monitoring.

4.1.2 Neuroprostheses Technology

Neural prostheses, or neuroprostheses, are neurotechnologies used to substitute or restore lost sensory, motor, or cognitive functions. Neuroprostheses can target peripheral or central nervous system structures.

Sensory neuroprostheses use neurostimulation technologies to recreate sensations by transducing external signals into spatiotemporal stimulation patterns targeting specific sensory regions of the nervous system. Remarkable examples of such neurotechnologies are cochlear and auditory brainstem implants, which can restore functional sensation of sound in people with profound hearing loss by stimulating the auditory neurons or the auditory region of the brainstem.

4.1.3 Brain-Machine Interface (BMI) Technology

BMIs are neurotechnologies that create a direct, artificial link between the brain and external devices (or within the body with electrical stimulation), allowing users to control movement and/or devices, sense the external world, and/or learn to self-regulate brain functions. The artificial link created by a BMI might be unidirectional or bidirectional. Unidirectional BMIs use neural interfaces that either read or write information from or into the brain, while bidirectional BMIs use neural interfaces to concurrently read and write information from and into the brain (Figure 2).

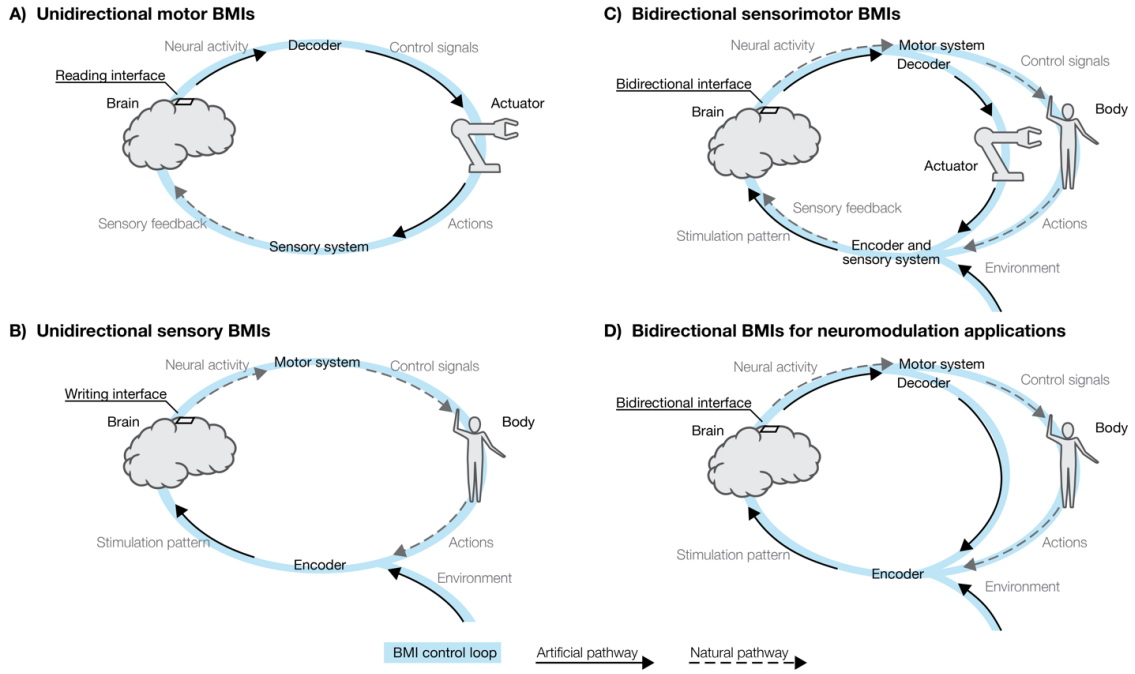

Figure 2. Unidirectional and bidirectional brain-machine interfaces (BMIs). A) *Unidirectional motor BMIs*. A reading neural interface is used to extract control signals from the brain activity and control an external actuator. B) *Unidirectional sensory BMIs*. A writing neural interface is used to induce sensations by stimulating sensory regions of the brain. C) *Bidirectional sensorimotor BMIs*. Neural interfaces are used to allow users to concomitantly feel and control external devices. D) *Bidirectional BMIs for neuromodulation*. Neural interfaces are used to extract volitional control signals and to modulate brain functions.

Classic examples of unidirectional BMIs are *motor* and *sensory* BMIs. Motor BMIs seek to measure the neural signals underlying intentions and to translate these signals into control commands for operating external devices (Figure 2A). These BMIs hold great potential to restore independence in people with motor disabilities, by allowing them to control assistive devices directly with their thoughts. Pilot clinical studies have demonstrated this potential, with BMI systems that allowed people with tetraplegia to control robotic arms, exoskeletons, computer cursors, and even their own paralyzed limbs through electrical stimulation.[21,22, 23, 24] Sensory BMIs encode external stimuli into stimulation patterns to artificially induce sensations. These systems have potential to restore lost senses, such as vision or hearing (Figure 2B).

S*ensorimotor BMIs* combine sensory and unidirectional motor BMIs to create a bidirectional link (Figure 2C). Sensorimotor BMIs have been shown to outperform unidirectional motor BMIs that rely purely on visual feedback to close the control loop.[25, 26] For example, BMIs that allow their users to both control a robotic limb and perceive the associated tactile and proprioceptive feedback information show possibilities for finer control and better embodiment.

In addition to sensorimotor BMIs, bidirectional systems have vast applications in neuromodulation therapies, rehabilitation therapies, and potentially for augmentation uses. An increasing number of BMIs target higher-order cognitive functions (such as language, memory, or attention) or seek to create closed-loop neuromodulation therapies (Figure 2D). The key to developing such closed-loop neuromodulation therapies is sensing of endogenous neural activity and using this in a control loop to precisely stimulate and/or regulate the same or another neural activity (see above for examples of bidirectional BMIs in this scenario).

4.2 Next Generation Closed-Loop Neurotechnology Development

Next generation closed-loop neurotechnology will build on current technologies in order to further focus on measuring neural signals from other areas of the nervous system, decoding these signals through advanced algorithms, and then stimulating as needed to affect a therapeutic or augmentative intervention, becoming more autonomous and adaptive to the requirements of the therapy as well as responsive to feedback obtained from the individual user over time. These concepts align with the goals of new research investigating the use of machine learning methods to control electrical stimulation in the spinal cord, which can also be translated to BMI systems.[27, 28]

The development of generalized bidirectional closed-loop neurotechnologies with multiple inputs and outputs that can operate as autonomously as possible is a perceivable goal in the near future. Milestone developments over the next 10 to 20 years would build on current technology and transition through the following three phases:

- Existing Technology: System gathers data over time; very limited continuous sensing with limited means of modifying stimulation to the nervous system as needed based on neurofeedback.
- Phase 1: Evolution of better sensor capabilities for feedback as well as for understanding downstream effects of stimulation will assist in creating more accurate models of how information travels downstream.
- Phase 2: Evolution of stimulation technologies that allow for superior spatial and temporal selectivity. Together with a better understanding of how information is processed in the nervous system, better stimulation technologies will be essential to advance the development of sensory BMIs and neuroprostheses that recreate rich sensory experiences and to develop next generation personalized neuromodulation therapies. More detailed data will promote access to improved model-based control schemes that will be able to act and better inform algorithm development and training as well as optimize input/output.

- Phase 3: Closed-loop systems will be more self-adaptive and autonomous and will require safe adjustments to parameters. The controller will be connected to an actuator that delivers an intervention through multiple pathways to a precise target, which has a downstream effect on a number of systems. Development of such a system requires a better understanding of dynamics, environmental parameters and effect, as well as how the body and target interact. Figure 3 builds on current capabilities to show the potential evolution of next generation closed-loop systems that gather sensor data from multiple points over longer time scales, including non-neural signals.

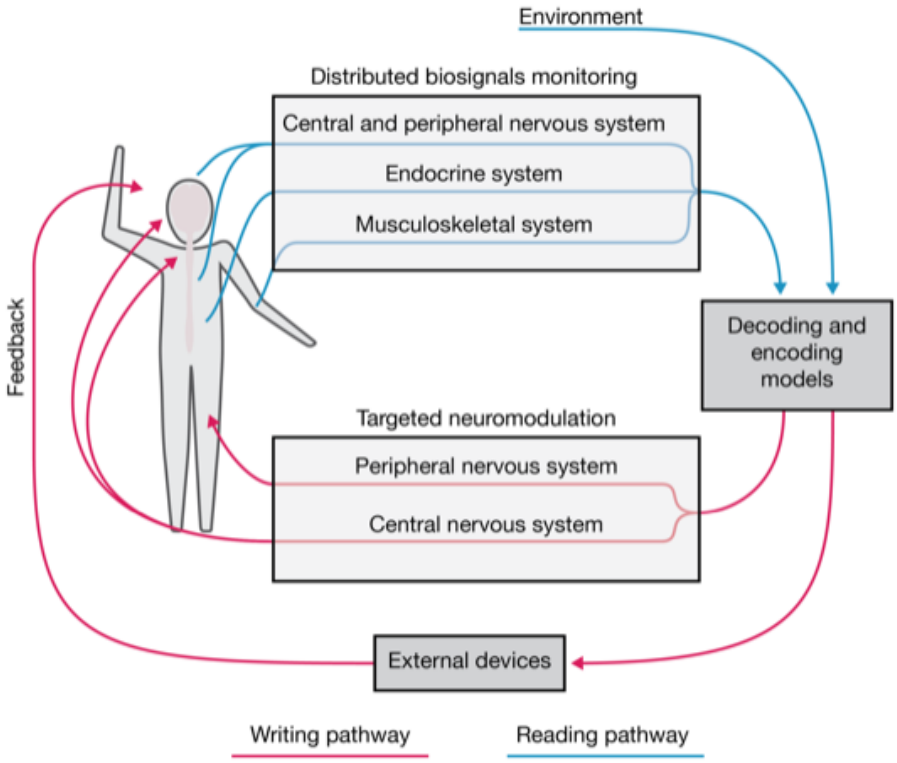

Figure 3. System design for 10-year horizon. A wide range of biosignals will be continuously monitored (at different timescales) to obtain a holistic view of the user physiological and/or pathophysiological state. Sensors will be used to measure neural signals generated across the central and peripheral nervous system, hormones and other biochemicals, as well as body kinematics and dynamics. External inputs will also be exploited to infer the user state and/or intentions. Decoding and encoding models will use this rich set of inputs to deliver targeted neuromodulation therapies and/or to allow high-throughput control of external devices.

Accessing the peripheral and/or autonomic nervous systems of the patient has the potential to make a given therapy more effective, which would be a significant value add for patients, clinicians, and the biomedical device industry. The gut, for example, contains dense neural layers. There is also the possibility of targeting with sensors that detect chemicals such as cortisol, which may grant access to what is missed by shorter timescale loops and provide feedback that would allow for stimulation as needed. Potentially, rich data can be obtained from the constellation of signals within the autonomic system; addressing incumbent challenges in encoding and decoding would enable a next generation closed-loop device that

incorporates data from the PNS/ANS to provide therapeutic and augmentative solutions beyond what is currently available.

4.3 Next Generation Closed-Loop Neurotechnology Applications

Next generation closed-loop neurotechnologies will offer therapeutic and rehabilitative options as well as augmentative capabilities. Potential applications include restoring movement function after neural injury or disease, providing functional cures for neurological diseases, treating memory disorders, treating neuropsychiatric disorders, increasing learning speed and ability, intuitively controlling assistive devices while receiving rich biomimetic feedback on the actuator, decoding language from brain signals for speech neuroprostheses, and offering devices that can both sense and stimulate activity in our sensorimotor system—changing the way our bodies interface with the world for both clinical and general consumer applications.

Any development of closed-loop neurotechnologies for therapeutic and/or augmentative applications should both serve to fill a need and deliver a high-impact solution (e.g., technologies that enhance memory function might also serve as a therapeutic treatment for diseases such as Alzheimer's). As emerging technologies, the key will be to coordinate value add for the stakeholder (clinician, patient, government agency) while minimizing potential harm (Figure 4). Targeted solutions for control of medication-resistant epilepsy and seizure currently in development and use, such as the NeuroPace RNS System, fulfill these requirements.

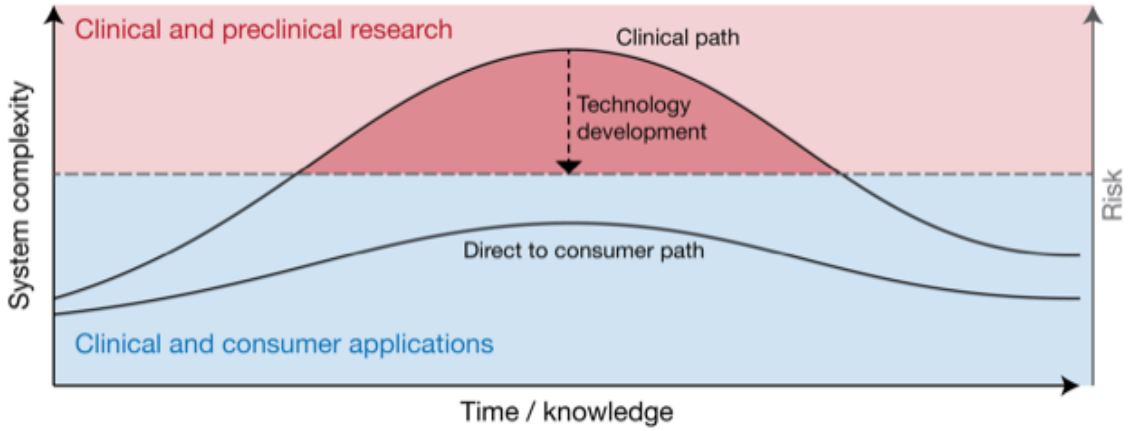

Figure 4. Clinical path vs. direct to consumer for technology development in relation to complexity and risk over time.

In the future, closed-loop neurotechnology devices have the potential to provide viable solutions in areas where pharmaceutical treatments have variable and often, low positive, results. These solutions could expand personalized medicine by sensing electrical signals throughout the body, taking measurements of molecular physiology, and intervening with

electrical stimulation delivered directly to the nervous system (e.g., spinal cord through epidural stimulation or intraspinal microstimulation,[29] as well as the PNS).

One example that has a potential for high impact is closed-loop control of bladder control, especially in people with paralysis.[30, 31] Bladder continence and voiding both require coordination of the sphincters and bladder wall contractions/relaxation. Feedback of bladder fullness and urethral sphincter function would be useful for controlling a neurotechnology targeting voiding and continence control.[32]

Additionally, development of a closed-loop system for general psychiatric therapy encompassing the orbitofrontal cortex (OFC) and the brain-body axis has the potential to provide therapeutic benefits for complexes such as addiction, anxiety, obsessive compulsive disorder (OCD), schizophrenia, eating disorders, and depression. This type of intervention is highly generalizable and could be adapted to promote or suppress a wide range of behaviors. This means that the treatment is highly personalized and symptom-driven as opposed to being generic for all subjects with a given diagnosis, offering significant value as a more personalized treatment approach.

4.4 Applications by Industry

Table 1: Potential Industry Applications for Closed-Loop Neurotechnologies

Medical	*Clinician and direct-to-consumer therapeutic devices to diagnose and treat disease.*
Wellness	*Consumer devices used for improving general wellness, including mood, memory, cognition, and pain.*
Education	*Cognitive and learning enhancement devices for use in the classroom and training.*
Workplace	*Devices that monitor and enhance efficiency, safety, and promote skills learning.*
Military/National Security	*Devices that support military engagement and enhance physical and mental ability.*
Sports	*Devices that enhance and improve physical performance and monitor physical well-being.*
Consumer Devices/ Electronics	*Devices that enable computer and other electronics control (e.g., phone); virtual and augmented reality devices assisted by brain control, silent speech, etc.*

5. Design Drivers and Trends

Traditional drivers for closed-loop systems for neural control have been therapeutic applications, including but not limited to attempts to correct and/or restore function in cases of movement disorders and spinal cord injuries (neural prosthetics, neural rehabilitation), and interventions and potential cures for neurological diseases such as epilepsy and Parkinson's disease. Other applications are potentially augmentative, and include investigating solutions for memory and learning enhancement (these also hold therapeutic value), military/defense applications, as well as consumer applications in wellness (basic therapeutics such as mood enhancement) and entertainment (gaming and virtual reality).

Neuroscience, and particularly neuroscientific psychiatry, is moving toward circuit-based understanding of disease and disorders. The opportunity to gain further knowledge about the brain and how it functions has been and will continue to be a key driver for innovation and transformation of the field. Non-profit science institutions and initiatives along with funding agencies including the NIH and DARPA have placed emphasis on decoding of the brain. Next generation closed-loop devices offer a unique opportunity to learn from recorded signals and stimulation of the brain through projects such as ElectRx and BG+. DARPA brain interface projects[33] including Next-Generation Nonsurgical Neurotechnology (N3), Neural Engineering System Design (NESD), Restoring Active Memory (RAM) and RAM Replay, Systems-Based Neurotechnology for Emerging Therapies (SUBNETS), Targeted Neuroplasticity Training (TNT), and Hand Proprioception and Touch Interfaces (HAPTIX) aim to support neurotechnology development and translation.[‡] In 2019, six teams were chosen as part of the N3 project to develop high-resolution bidirectional BMIs[34] using diffuse optical tomography, magnetic fields, nanoparticles, and ultrasound among other techniques.

A prevailing trend for design of closed-loop neurotechnology is toward becoming less invasive to minimally- or non-invasive as stakeholders and industry continue to make these demands (i.e., DARPA requirements and clinician preference, as well as direct-to-consumer designs). However, it is of particular importance that devices show proven efficacy for treating disease with minimum side effects, which in part requires becoming more precise with dosage as well as target areas for stimulation (e.g., precision electronic medicine[35]) regardless of level of invasiveness. Building on neurostimulation treatments already approved by the FDA such as transcranial magnetic stimulation (TMS) and electroconvulsive therapy, research is underway that would combine closed-loop EEG with TMS, for example, in order to promote precision

[‡] *N3 aims to develop high-resolution technology that will read and write to multiple brain locations without implantation; NESD is intended to fund efforts to improve signal resolution and bandwidth between implantable neural interfaces and devices; RAM aims to support development of a fully-implantable neural device that will aid in formation and restoration of memory; RAM Replay supports efforts to develop novel computational methods to identify brain those brain components vital for memory and recall; SUBNETS is intended to create closed-loop implantable therapeutic and diagnostic devices for treating neuropsychological illness; TNT aims to pursue platform technology that would advance cognitive skills training through activation of peripheral nerves and support neural connections; the goal of HAPTIX is to create wireless, modular neural micro-interfaces that work with external modules in order to deliver sensations to amputees.*

target dosage. One of the inhibitors to adoption of currently available therapeutic neurological device systems, such as deep brain stimulation (DBS) systems, is the variability of side effects as well as difficulty in reproducing results across patients. Next generation closed-loop devices designed to record signals in real time and respond therapeutically as needed will push the reliability and success of these therapies further.

In order to be competitive with pharmaceuticals as therapeutic interventions, surgery and implants will need to be kept to a minimum whenever possible. Having a safe, easy to implement device solution that is as simple as a needle is essential, otherwise pharmaceuticals likely will be preferred. Improved and miniaturized electrodes and components consisting of soft, stretchable, biocompatible materials that are more stable over the long-term will open avenues to new experimental techniques. The current trade-off between invasiveness and spatiotemporal resolution (i.e., non-invasive electrodes such as EEG provide less signal information compared with ECoG, intracortical, or deep brain recording electrodes) will guide the push for alternative surgical approaches for implantable devices such as injecting ECoG arrays or microthreads through small holes (see, for example, Neuralink).

Sensors that further expand to encompass signals from the CNS, PNS, and ANS will be crucial to next generation devices. Using these signals to optimize the control signals in real time will maximize effectiveness and aid precision. Non-invasive devices that incorporate nerve stimulation serve as case studies on the effects of stimulation on neural systems, including vagal, occipital, or transcutaneous spinal cord stimulation.[36, 37, 38] The trigeminal nerve stimulation (TNS) device developed by NeuroSigma for treatment of pediatric ADHD and approved by the FDA in early 2019[39] is one example.

Demand for coordination of closed-loop devices with artificial intelligence (AI) and machine learning to assist with fine-tuning systems with higher channel counts, algorithm development and training, data management, and feedback will also determine future design and implementation. Increases in cloud computing capabilities will assist with managing the data, although establishing protocols for security and privacy will be of critical importance. Establishment of neural data repositories, such as Neurodata Without Borders[40], will assist in moving the field toward standardization and reproducibility in testing and clinical trials, aiding in regulatory approvals and translation of next generation devices. In addition, evolving FDA guidelines and the costs of development will guide the future of neurotechnology design choices and translation paths.

6. Design Challenges

Significant challenges exist in moving from current closed-loop systems to designing and building a future system[41] that further taps into the body's nervous systems in areas of technology (e.g., access, sensing, targeted and distributed CNS and PNS stimulation); system integration (e.g., multiple distributed CNS and PNS contact points, the need for robust wearable computing); decoding (e.g., multiple embedded loops operating at different time scales, difficulty in establishing ground truth); and regulatory approval and clinical trials. Other approaches, such as the need to access and/or sequence genomic information to improve system design and feedback would present additional challenges.

Multiple design challenges are also inherent in migrating from devices that are rather large to devices that are vanishingly small and/or minimally- or non-invasive as well as moving from animal models to human models. Other barriers include identifying where to stimulate and how to do so in order to deliver crucial therapies and generate biomimetic neural signals that 'speak' the same language as the nervous system.[42] In addition to understanding neural circuits, this requires identification of the expected responses from the neural stimulation.[43] Models of this process are necessary to build control systems effectively, as well as to determine optimal stimulation parameters including amplitude, pulse width, duty cycle, frequency, waveform, and electrode configuration.

Closing the loop also means having to deal with potentially unanticipated events. Using AI to help develop predictive models as well as rigorous and standardized testing procedures will be vital in anticipating and preparing for possible reactions. Working with regulatory agencies to expand possibilities for clinical trials and approval of devices will be necessary for successful market translation of devices.

6.1 General Design Requirements

Next generation closed-loop neural devices need to:

- Function at a minutely- or non-invasive level or, if surgery cannot be avoided, present minimal trauma and fast healing times.
- Provide intuitive clinical and user interfaces.
- Offer improved sensing and stimulating capabilities at multiple and varied locations (encompass multi-modal/multidimensional/multi-state estimation).
- Be compatible with physiology as well as have the ability to adapt to the body's changing physiology (feedback-controlled).
- Provide secure and private data collection and storage.
- Demonstrate proven safety and comfort in order to promote widespread adoption.

6.2 Technology Challenges

6.2.1 Scale

There are significant design challenges when moving from animal models to humans as well as biocompatibility when moving from large, invasive devices to small, minimally- or non-invasive devices. Smaller sizes must still be robust enough for implementation (e.g., implanted by surgeon; viable for long-term use).

6.2.2 Materials

Stretchable, soft, stable materials are needed that will remain viable over longer terms. Biocompatibility is required to avoid detrimental encapsulation. Efforts to avoid encapsulation include reducing mechanical mismatch and coating the electrodes with growth factors, anti-inflammatory drugs, or peptides.[44] New fabrication processes and methods are critical for production and availability. Ageing standards and access to ageing facilities needs to be improved in order to standardize materials for long-term devices. Also, a major challenge of implantable devices is a lack of direct knowledge of the range of effects that the human body has on implanted electrodes (e.g., Utah Array).

- The field lacks techniques that can be performed *in vivo* to inspect implanted materials, leading to speculation from indirect methods such as impedance measurements and review after explantation.
- Animal models have shown to produce significantly different results than humans, specifically for the Utah array.

6.2.3 Electrodes and Sensors

Current electrode designs are limited in scale, number, and longevity. Standardization and miniaturization, as well as biocompatibility, are key challenges. Improving the stability of both non-invasive and invasive neural interfaces will be crucial in the near future to improve performance; surface electrodes suffer from displacement and require a recalibration stage to account for inconsistent placement, and implanted arrays tend to drift. Many of the sensors available for closed-loop control are external and may have to be incorporated into clothing or require frequent donning and doffing. While some sensors, such as EMG, can be implanted, they are prone to lead wire breakage. Chronic hormone/neurotransmitter sensors do not exist and chronic organ state sensors are limited (e.g., pressure).

Non-invasive electrodes and sensors will be crucial to promote usability; however, significant design challenges remain.

- High electrode contact impedance usually necessitates a conduction enhancer (e.g., gel) which does not lend itself well to usability. Better dry electrodes need to be developed.
- Good electrode contact must be ensured if non-invasive stimulation is performed over an extended period of time in order to keep impedances (and electrode-to-skin contact temperatures) low.
- Non-invasive stimulation requires higher voltage, which will require the hardware to be larger. In addition to comfort and safety concerns, the high voltage will increase

stimulation artefacts in any sensitive recording equipment, presenting challenges for recording hardware stability and signal processing.
- Leveraging commercially available technologies (smart watches, textiles, etc.) can help reduce development costs and expedite development.

6.2.4 Recording

Improvements in wireless options, processing speed, and sensitivity to noise are needed. Multiple electrodes capture each signal differently, for example, LFP recordings are fairly stable but difficult to interpret.

6.2.5 Computation

Machine learning and adaptive algorithms are needed for continuous adaptation using a range of multiscale models (electrical, chemical, behavior) such as adaptive inverse control, reinforcement learning, and hierarchical optimal control. How data should be bound and evaluated will need to be determined; current data safety monitoring boards may not have the expertise to evaluate this type of data in order to comply with FDA rules, and these rules tend to fall behind actual technology development. Since neurotechnology should be designed for long-term use, field updating of algorithms will be required. Other considerations include:

- Devices must be interoperable, necessitating a unifying software framework.
    - Leverage proven algorithms for different use cases.
    - Enhance a given algorithm with new data or data type.
    - Use a given algorithm and input to control a different end effector.
- Individual teams will often have a large amount of data but only from a few users. Data must be shared effectively to allow for more generalizable, robust algorithm development. Along with data security and privacy concerns, there exists a unique set of business interest concerns that must be addressed since data is valuable.
- Innovators need to consider the trade-offs between computational complexity and the ability to run computations on portable devices. Complicated algorithms that provide state of the art results may not be the most practical if they prevent portability.

6.2.6 Robustness

Closed-loop neurotechnologies need to be designed for safe, long-term (ideally lifetime) use and be resistant to failure, with minimal damage to tissue over time. Devices should be equipped with a minimal operational mode, i.e., a fail-safe mode, if an unknown state arrives. Thorough documentation of system disruptions (electrostatic discharge, cell phone interference, etc.) will enable development of techniques to improve longevity and robustness of devices.

6.2.7 Power

Next generation devices require improved battery life and reliable methods of power delivery to active electronic microchips, sufficient computational power to handle large amounts of data (exact data quantities unknown), and wireless power transfer without heating. New ways to generate power (e.g., combining modalities, harvesting energy from internal organs/muscles) will be necessary.

6.2.8 Multiscale Signal Processing, Modeling, and Control

Neurophysiology knowledge (e.g., prioritization of the variables to be measured and best controlled) will need to be employed to specify engineering constraints in model validation, and toward measurements, modeling, and manipulation of physiological variables. Addressing the spatiotemporal structure of spike trains, LFPs, and EMG, for example, requires development of advanced algorithms that are more robust and extract specific information from the data, e.g., multiscale modeling methodologies in functional spaces, and new generative models that learn how to explain the input data. The community must continue developing techniques to extract information from raw data, including alternatives to the traditional approach of recording neural spiking and LFPs from intracortical MEA recordings or EMG from high-density surface electrodes. Even with advances in computational speed, constant consideration must be given to the computational load required for processing data to extract the most useful information.

6.2.9 Communications

System design of secure, stable, and reliable wireless communication outside of controlled environments is a key challenge, along with managing the role of cloud computing and data storage. Integration of information from external sensors (environment) needs to be better understood. Other challenges include design and development in areas of:

- Wireless transcutaneous (also with peripheral implants) and/or transcranial bidirectional data flow
    - Customized network communication protocols for high speed read/write with minimal loss of data packets
    - Network hardware and protocols to enable adaptive targeting of key neural circuits
    - Power and safety limits
    - Cybersecurity
- Real-Time Neural/Biosignal/Encoding
    - Wearable, mobile computational hardware (programmable embedded system)
    - Neurocomputational decoding/encoding models in real time

6.2.10 Safety and Reliability

Few devices have target verification providing information as to whether or not the device is performing as expected; validating that the system is responding appropriately is key. Other challenges include ensuring minimal tissue damage, simpler and less-invasive surgical implantation techniques, and reliability for long-term 24/7 chronic use (device robustness, hermetic packaging, etc.). Devices must be designed with the option for user override and expert/surrogate override and parameters need to be clearly defined. Responsible use and meaningful assent guidelines should be in place. Risks must be mitigated for all known use cases, but due to the nature of neural therapeutics as assistive devices, the number and variety of use cases is vast. Special consideration of study designs must be made to assess the different variety of risks that can be encountered for each use-case, understanding that many risks may not ever be fully understood and characterized. Innovators and manufacturers need to improve transparency of these shortcomings and limitations of the technology, particularly for the

targeted user group (e.g., the user drops a knife on their foot while using a BMI system to control a prosthetic hand).

6.2.11 Data Security and Privacy

Guidelines for data management, including who owns the data, how it is shared, and how ownership is controlled, as well as guidelines for patient access to data, should be standardized. Authentication should be required to access, add, and generate the data. Challenges also remain in facilitating data storage and security, as well as with managing data spread, patient privacy and anonymity, and general cybersecurity.

6.2.12 Regulatory

Current regulatory approval processes need to further adapt without impacting safety. Clinical trial design and testing procedures also need to adapt in order to test dynamic/adaptive systems where it is impossible to test all the states, and better computational, *in vitro*, and animal models are required. Standardization of trial variables and materials are needed to address issues of reproducibility. Guidelines on augmentation and consumer protection should be in place prior to device translation. All closed-loop neurotechnologies should take into account the FDA Patient Engagement Guidelines.

6.2.13 Ethical

Ethical concerns are inherent to questions of controlling assess, sharing data, selling data, and bias-free models as well as the boundaries of use for both invasive and non-invasive technologies. Clinical ethics and patient care ethics can serve as starting guidelines but need to be expanded to incorporate the complexity of closed-loop neurotechnologies. Industry standards should also provide guidelines on the means for opting in and out of studies, post-trial/study management and care, and procedures for device maintenance beyond the life of the commercial venture. Just and ethical use standards for closed-loop neurotechnology need to be drafted, particularly for commercial and direct-to-consumer devices. Special consideration needs to be taken with regards to not misleading potential study participants by presenting demonstration materials (e.g., videos in the media) without first helping them to understand the true state of the technology.

- Many studies require high-risk procedures, such as intracranial electrode implantation.
- Researchers must be fully transparent about the shortcomings of the technology, what the experience will actually be like for the study participant, and what the likelihood is of the technology benefiting the participant or anyone else.
- Informed consent forms can be seen as mostly legalistic rather than actual statements of liability and technology limitations. Researchers should present realistic expectations in a clear and concise manner to ensure participant understanding.

6.2.14 Translation

Challenges remain for prototype development procedures, justifying cost of therapeutic devices (computing vs. surgical) as well as securing investment capital. Sharing models of business cases focusing on cash-flow generation, market opportunity identification, and recommended pathways for translation would be helpful. Standardization of materials and device testing

could assist in lowering time and cost factors. Business models must be developed that specialize in the commercialization of high-risk neurotechnology. As an increasing number of neurotechnology companies fail, there will be fewer investments in these companies because they will be seen as too high risk, thus negatively impacting the whole field. These business models need to be determined early on in development. Neurotechnology to be used for a medical benefit requires a clear and efficient path for financial coverage, which involves effective and transparent communication between stakeholders—primarily the payers and neurotechnology innovators.[45]

- Early discussions with payers to determine optimal clinical path (e.g., trial designs, outcome measures, etc.) that align with payer's expectations.
- Innovators need to discuss price points of technologies with payers to ensure their devices meet the payer expectations.
- A comprehensive review of the developing technology by payers throughout clinical testing would help align expectations and goals to ensure eventual coverage.
- Innovators need to do the work to demonstrate that their technologies take cost out of the system in order to build the trust of payers that their technologies will improve the quality of life and reduce overall medical costs.

6.2.15 Usability

Usability is a key technology challenge that is often overlooked throughout the majority of the development phase. Usability challenges include the requirement for a caregiver to operate the device; patient requirement for device assistance must be minimized as well as set up and training time and effort. The device should not be obtrusive and cause the user to be stigmatized. Formal usability tests need to be conducted early in the development process as it is difficult to predict how people with disabilities use devices without their input.

6.3 Additional System Challenges

6.3.1 Readout: Sensing, Biomarkers, and Feedback

For a closed-loop system that is designed to gather feedback from the brain and/or CNS/PNS/ANS, sensors will be needed that can access chemical targets including molecules, neurotransmitters, and hormones. Feedback should also include body physiology (e.g., blood pressure, pupil dilation, temperature, pH, electrocardiogram, electromyography, immune response) as well as environmental factors. There is also the possibility of factors outside the system that unknowingly feed back into the system and affect response. In addition, how best to design a sensor that adapts to body state (e.g., sleep) is still unknown.

6.3.2 Write In: Targets

Determining how best to precisely and successfully write-in (electrical, optical, magnetic) and where to do so in order to create biomimetic sensory feedback signals and also increase functional plasticity and reduce maladaptive plasticity in the system is a significant challenge.

6.3.3 Encoding/Decoding

Because of the large amount of data generated by these models, questions on how that data should be bound and evaluated remain. Current data safety monitoring boards may not have the expertise to evaluate this type of data in order to comply with FDA rules.

- Collecting sufficient data to train the 'long time-scale' decoder (spanning space/range, training time).
- Developing a principled control policy to update the internal model with ‘smart’ adaptation for mitigation.
- Creating a real model of this system requires addressing these multiple nested challenges:
    - How to establish an appropriate ground truth,
    - How generalizable will the decoder be—will training at home or in the clinic generalize to the outside world,
    - How will autonomic space be sampled—clinical populations may have a reduced autonomic space (e.g., depressed patients will only have a depressed state), and
    - Challenges in matching sensing data to the neural data (e.g., the dynamics of mood state and neural activity could occupy very different temporal domains).

6.3.4 Controller and Timescales

An ideal controller for a closed-loop system would be flexible, programmable with user and expert input over time, upgradable, and adaptive. One approach would be to utilize computational models. However, many assumptions collapse under the ideal properties of the controller—timescales on which we act, timescales on which the body responds, as well as timescales of plasticity. Alternatively, machine learning methods such as reinforcement learning could be used to provide automatic and adaptive control.[46] Reinforcement learning works well in stochastic environments, and recent methods demonstrate the use of many sensor signals, including EMG and ground reaction forces, which can be noisy.

- Memory: Little is known about what will happen in certain cases and across long time scales so collection of data from many patients continuously is required to see the changing baseline and then appropriately update the model.
- Manage unintended consequences: Currently unable to predict what data may be important for solving new challenges. Unintended consequences may actually be improvements to both the patient and scientific knowledge.

7. Technology Enablers and Solutions

As closed-loop neurotechnology is driven forward, the barrier of entry to the consumer is lowered, especially as more minimally-invasive and non-invasive devices are developed. The clinical round enables initial opportunity to advance the field but there might not be a financial justification for fulfilling a medical/clinical need without the additional support a consumer product provides. Essentially, most technologies are initially designed to help or fill a need, and consumer or military defense demand will likely be driving some applications (e.g., augmentative).

Other enablers include current growth in the variety and design advancements of sensor and electrode capabilities, as well as improved materials. Development of smaller, softer, stretchable, low-power electrodes and sensors that are viable long-term is key to next generation devices. Solutions to encapsulation with improved biocompatibility will promote development of new applications and devices.

Incentives put in place for investment in packaging materials for electrodes and implants will help to increase standardization and robustness of components. Fabrication and design of materials must eventually evolve to further integrate with chemical and optical sensors for human subjects versus animal models.

Alternative approaches including optogenetics, ultrasound, and combining modalities of technologies will lead to more precise and less invasive technologies. Advances in wireless communication and cloud computing will help with management of the large data captures from multiple sensors. Development of multi-modal capabilities for generating power with less heating, including using energy from the body, will assist with sensor capability and longevity.

Machine learning and open data sharing will contribute to advancing the creation of adaptable electronics and more standardized solutions. Generalized algorithms that search recorded brain activity for viable signals may lead to new discoveries. Advancements in genomics will further extend knowledge of the intricacies of individual neural plasticity and excitability, aiding in patient trials. Additionally, as knowledge of the brain network increases, including the role of glial and other biological components, technology designs will become more adaptable to the nervous system environment.

Examples of some current efforts that likely will prove integral to development of next generation devices include the following:

7.1 Advanced Electrodes and Sensors

- Small, soft, and stretchable sensors and electrode arrays that mimic cellular or subcellular structures[47,48]
- Small (on the order of microns) carbon fiber microelectrodes offer precise positioning, less bleeding, and alignment of fibers for optogenetics

- Microwire electrodes[49] (e.g., NeuroRoots[50]) that are needle-like, easy to implant, and more stable
- Soft electrodes (e.g., e-Dura[51])
- Neural dust—wireless millimeter-sized devices powered by ultrasound[52]
- Neural mesh—optimizing interface between implant and neural substrates through ultra-flexible 2D scaffolds[53]
- Stentrode[54]—minimally invasive electrode array on a stent implanted in a blood vessel
- Injectrode[55]—an injectable neural stimulation electrode consisting of liquid composites
- Double-sided electrodes
- Chemical sensors and probes with increased sensitivity
- Optical sensors and optical fibers
- Semi-synthetic biosensors

7.2 Improved Stimulation Technology

- Temporal interference[56]
- Holographic optogenetic stimulation[57, 58]
- Ultrasound stimulation[59]

7.3 Improved Materials/Biocompatibility

- Hydrogel electronics
- Organic coatings
- Conductive polymers, micrometallization, polymer electrodes coated with bioactive molecules
- Graphene (porous, transparent)
- Polycrystalline diamond

7.4 Computation and Artificial Intelligence

- Combination of machine learning and highly customizable adaptive machine learning algorithms
- Improved training scenarios and computational models
- New models for animal to human device transitions
- Open data repositories
- Automated machine learning algorithms for identifying optimal stimulation

7.5 Communication

- Improved wireless communication between sensors
- Advanced data security and privacy protocols

8. Conclusions

Although still in its infancy, development of closed-loop neurotechnologies is in part driven by the prevalence of neurological and psychiatric disorders, many of which do not respond well to pharmacological treatments or do not have other viable treatment options. The potential to provide proven therapeutic devices that address chronic depression, post-traumatic stress disorder (PTSD), motor impairments caused by SCI and stroke, and diseases such as epilepsy, Alzheimer's, and Parkinson's will guide technology development in the near future. Closing the loop on such devices will offer more precision and personalization, as therapeutic stimulation becomes better designed to respond more directly to the patient's own neural physiology.

Tangentially, the search for avenues to successfully integrate prosthetic devices with the body and/or restore sensory and motor function, as well as enhance and restore higher order cognitive functions such as memory, speech, attention, and learning, contributes to the prevalence in research and development of next generation closed-loop neurotechnologies. Although the majority of current efforts lack the robustness and longevity for translation into clinical solutions, continued investment along with advances in material design, standardization of components and testing procedures, advances in adaptable machine learning algorithms, as well as efforts to combine methods and modalities to create peak effectiveness with closed-loop neurotechnologies will promote device translation and grow market appeal. Addressing other technological challenges identified here will also support viable solutions for therapeutic and consumer applications.

Ultimately, next generation closed-loop devices will reimagine the partnership between the brain and body's nervous systems, with the potential to provide effective precision electronic medicine and drive new consumer applications.

9. Contributors

IEEE Brain would like to acknowledge the assistance of those listed here in development of this white paper. In addition, feedback from key stakeholders provided essential input for revised content.

Jose Carmena, University of California, Berkeley, IEEE Brain Co-Chair
Paul Sajda, Columbia University, IEEE Brain Co-Chair
Jacob Robinson, Rice University, IEEE Brain Co-Chair
Amy Orsborn, University of Washington
Samantha Santacruz, University of Texas, Austin
Ashley Dalrymple, Carnegie Mellon University
Emanuele Formento, University of California, Berkeley

Participants in the September 2018 IEEE Brain Think Tank

Sliman Bensmaia, University of Chicago
Jose Carmena, University of California, Berkeley
Rui Costa, Columbia University
Joseph Fins, Cornell University
Sara Goering, University of Washington
Daniel Gonzales, Rice University
Aysegul Gunduz, University of Florida
Sin-Kuen Hawkins, IEEE Brain
Linbi Hong, Columbia University
Surya Ganguli, Stanford University
Judy Illes, University of British Columbia
Brian Litt, University of Pennsylvania
Caleb Kemere, Rice University
Michel Maharbiz, University of California, Berkeley
Chet Moritz, University of Washington
Karen Moxon, University of California, Davis
Arto Nurmikko, Brown University
Amy Orsborn, University of Washington
Paul Sajda, Columbia University
Bijan Pesaran, New York University
Jose Principe, University of Florida
Jan Rabaey, University of California, Berkeley
Grace Rigdon, IEEE Brain Conferences
Jacob Robinson, Rice University
Samantha Santacruz, University of Texas, Austin
Steven Schiff, Pennsylvania State University
Maryam Shanechi, University of Southern California
Kenneth Shepard, Columbia University
Vikaas Sohal, University of California, San Francisco
Fritz Sommer, University of California, Berkeley
Andreas Tolias, Baylor University
Joni Wallis, University of California, Berkeley
Cynthia Weber, IEEE Brain
Douglas Weber, University of Pittsburgh
Rafael Yuste, Columbia University
Theo Zanos, Feinstein Institute
Stavros Zanos, Feinstein Institute

IEEE Brain

Sin-Kuen Hawkins, Program Manager
Cynthia Weber, Project Coordinator

10. References

[1] https://braininitiative.nih.gov
[2] https://www.humanbrainproject.eu/en/
[3] https://brainminds.jp/en/
[4] Rao, R. Towards neural co-processors for the brain: combining decoding and encoding in brain-computer interfaces. *Current Opinion in Neurobiology* **55**, 142-151 (2019). doi: 10.1016/j.conb.2019.03.008.
[5] Cagnan, H., Denison, T., McIntyre, C. and Brown, P. Emerging technologies for improved deep brain stimulation. *Nature Biotechnology* **37**, 1024–1033 (2019).
[6] Frank, J., Antonini, M-J., and Anikeeva, P. Next-generation interfaces for studying neural function. *Nature Biotechnology* **37**, 1013–1023 (2019).
[7] Flesher, S.N. et al. Intracortical microstimulation of human somatosensory cortex. *Science Translational Medicine* **8**, 361ra141 (2016).
[8] Cervera, M. A. et al. Brain-computer interfaces for post-stroke motor rehabilitation: a meta-analysis. *Annals of Clinical Translational Neurology* **5**, 651-663 (2018).
[9] Wagner, F.B., Mignardot, J., Le Goff-Mignardot, C.G. *et al.* Targeted neurotechnology restores walking in humans with spinal cord injury. *Nature* **563**, 65–71 (2018). https://doi.org/10.1038/s41586-018-0649-2
[10] Anumanchipalli, G.K., Chartier, J. and Chang, E.F. Speech synthesis from neural decoding of spoken sentences. *Nature* **568**, 493–498 (2019). https://doi.org/10.1038/s41586-019-1119-1
[11] Bouthour, W. et al. Biomarkers for closed-loop deep brain stimulation in Parkinson disease and beyond. *Nature Reviews Neurology* **15**, 343-352 (2019).
[12] Yuste, R. et al. Four ethical priorities for neurotechnologies and AI. *Nature* **551**, 7679 (2017).
[13] Seligman, P.M. and Shepherd, R.K. Cochlear implants. In *Neuroprosthetics: Theory and Practice*, K. Horch & G. Dhillon (Eds). World Scientific Publishing: Singapore, 878-904 (2004).
[14] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/implanted-brain-computer-interface-bci-devices-patients-paralysis-or-amputation-non-clinical-testing
[15] Caylor, J., Reddy, R., Yin, S. et al. Spinal cord stimulation in chronic pain: evidence and theory for mechanisms of action. *Bioelectron Med* **5**, 12 (2019). https://doi.org/10.1186/s42234-019-0023-1
[16] Capogrosso, M., Milekovic, T., Borton, D. et al. A brain–spine interface alleviating gait deficits after spinal cord injury in primates. *Nature* **539**, 284–288 (2016). https://doi.org/10.1038/nature20118
[17] Parastarfeizabadi, M., Kouzani, A.Z. Advances in closed-loop deep brain stimulation devices. *J Neur Eng Rehabil* **14**, 79 (2017). https://doi.org/10.1186/s12984-017-0295-1
[18] Kuo, C. H., White-Dzuro, G. A., and Ko, A. L. (2018). Approaches to closed-loop deep brain stimulation for movement disorders. *Neurosurgical focus* **45(2)**, E2 (2018). https://doi.org/10.3171/2018.5.FOCUS18173
[19] http://www.cando.ac.uk/aboutcando/
[20] Bergey, G. K., Morrell, M. J., Mizrahi, E. M., et al. Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. *Neurology* **84(8)**, 810–817 (2015). doi:10.1212/WNL.0000000000001280
[21] Bouton, C. E. et al. Restoring cortical control of functional movement in a human with quadriplegia. *Nature* **533**, 247–250 (2016).
[22] Collinger, J. L. et al. High-performance neuroprosthetic control by an individual with tetraplegia. *Lancet* **381**, 557–564 (2013).
[23] Hochberg, L. R. et al. Neuronal ensemble control of prosthetic devices by a human with tetraplegia. *Nature* **442**, 164–171 (2006).
[24] Benabid, A. L. et al. An exoskeleton controlled by an epidural wireless brain–machine interface in a tetraplegic patient: a proof-of-concept demonstration. *Lancet Neurol.* **18**, 1112–1122 (2019).
[25] Lebedev, M. and Nicolelis, M.A.L. Brain machine interfaces: from basic science to neuroprostheses and neurorehabilitation. *Physiol Rev* **97**, 767–837 (2017). doi:10.1152/physrev.00027.2016
[26] Shanechi, M.M. Brain–machine interfaces from motor to mood. *Nat Neurosci* **22,** 1554–1564 (2019). https://doi.org/10.1038/s41593-019-0488-y
[27] Dalrymple, Ashley N., Roszko, D. A., Sutton, R. S., and Mushahwar, V. K. Pavlovian control of intraspinal microstimulation to produce over-ground walking. *J Neur Eng* **17(3)** (2020). https://doi.org/10.1088/1741-2552/ab8e8e

[28] Desautels, T. A., Choe, J., Gad, P., Nandra, M. S., Roy, R. R., Zhong, H., Tai, Y.-C., Edgerton, V. R., and Burdick, J. W. An active learning Algorithm for Control of Epidural Electrostimulation. *IEEE Transactions on Bio-Medical Engineering* **62(10)**, 2443–2455 (2015). https://doi.org/10.1109/TBME.2015.2431911
[29] Zimmermann, J.B., and Jackson, A. Closed-loop control of spinal cord stimulation to restore hand function after paralysis. *Front Neurosci* **8**, 87 (2014).
[30] Fowler, C. J., Griffiths, D., and de Groat, W. C. The neural control of micturition. *Nature reviews. Neuroscience* **9(6)**, 453–466 (2008). https://doi.org/10.1038/nrn2401
[31] Gaunt, R. A., and Prochazka, A. Control of urinary bladder function with devices: successes and failures. *Progress in brain research*, **152**, 163–194 (2006). https://doi.org/10.1016/S0079-6123(05)52011-9
[32] Sanford, M. T., and Suskind, A. M. Neuromodulation in neurogenic bladder. *Translational andrology and urology*, **5(1)**, 117–126 (2016). https://doi.org/10.3978/j.issn.2223-4683.2015.12.01
[33] https://www.darpa.mil/program/our-research/darpa-and-the-brain-initiative
[34] https://www.darpa.mil/news-events/2019-05-20
[35] Patel, S. R. and Leiber, C. M. Precision electronic medicine in the brain. *Nature Biotechnology* **37**, 1007–1012 (2019).
[36] Inanici, F., Samejima, S., Gad, P., Edgerton, V.R., Hofstetter, C.P., and Moritz, C.T. Transcutaneous electrical spinal stimulation promotes long-term recovery of upper extremity function in chronic tetraplegia. *IEEE Trans Neural Syst Rehabil Eng* **26**, 1272–1278 (2018).
[37] Hofstoetter, U.S., Krenn, M., Danner, S.M., Hofer, C., Kern, H., McKay, W.B., Mayr, W., and Minassian, K. Augmentation of voluntary locomotor activity by transcutaneous spinal cord stimulation in motor-incomplete spinal cord-injured individuals. *Artif Organs* **39**, E176-186 (2015).
[38] Gad, P., Gerasimenko, Y., and Edgerton, V.R. Tetraplegia to overground stepping using non-invasive spinal neuromodulation. In *9th International IEEE/EMBS Conference on Neural Engineering (NER)*, 89–92 (2019).
[39] https://www.prnewswire.com/news-releases/neurosigma-announces-fda-clearance-of-monarch-etns-system-as-first-non-drug-treatment-for-pediatric-adhd-300837050.html?tc=eml_cleartime
[40] https://www.nwb.org
[41] https://brain.ieee.org/brain-storm/designing-for-the-brain/
[42] Formento, E. et al. A biomimetic electrical stimulation strategy to induce asynchronous stochastic neural activity. *J Neur Eng* **17(4)** (2020).
[43] Capogrosso, M., Lempka, S.F. A computational outlook on neurostimulation. *Bioelectron Med* **6**, 10 (2020). https://doi.org/10.1186/s42234-020-00047-3
[44] Gaire, J., Lee, H.C., Hilborn, N., Ward, R., Regan, M., and Otto, K.J. The role of inflammation on the functionality of intracortical microelectrodes. *J Neur Eng* **15(6)** (2018).
[45] https://videocast.nih.gov/summary.asp?Live=22155&bhcp=1
[46] Edwards, A.L., Dawson, M.R., Hebert, J.S., Sherstan, C., Sutton, R.S., Chan, K.M., and Pilarski, P.M. Application of real-time machine learning to myoelectric prosthesis control: A case series in adaptive switching. *Prosthet Orthot Int* **40**, 573–581 (2016).
[47] Garcia-Sandoval, A. et al. Chronic softening spinal cord stimulation arrays. *J Neur Eng* **15(4)** (2018).
[48] Liu, J. et al. Syringe-injectable electronics. *Nature Nanotechnology* **10**, 629-636 (2015).
[49] Obaid, A. et al. Massively parallel microwire arrays integrated with CMOS chips for neural recording. *Science advances* **6(12)** (2020).
[50] https://neuroscience.stanford.edu/events/neuroroots-seamless-biomimetic-implant-long-term-brain-machine-interfaces-marc-ferro-0
[51] https://actu.epfl.ch/news/neuroprosthetics-for-paralysis-an-new-implant-on-4/
[52] Neely, R. M., Piech, D. K., Santacruz, S. R., Maharbiz, M. M., and Carmena, J. M. Recent advances in neural dust: towards a neural interface platform. *Current Opinion in Neurobiology* **50**, 64-71 (2018).
[53] Hong, G., Yang, X., Zhou, T. and Lieber, C. M. Mesh electronics: a new paradigm for tissue-like brain probes. *Current Opinion in Neurobiology* **50**, 33-41 (2018).
[54] John, S.E., Grayden, D.B., and Yanagisawa, T. The future potential of the Stentrode. *Expert Review of Medical Devices* **16(10)**, 841-843 (2019). DOI: 10.1080/17434440.2019.1674139
[55] https://engineering.case.edu/ebme/pathwaytopainrelief
[56] Grossman et al. Noninvasive deep brain stimulation via temporally interfering electric fields. *Cell* **169**, 1029–1041 (2017). http://dx.doi.org/10.1016/j.cell.2017.05.024

[57] Reutsky-Gefen, I., Golan, L., Farah, N. et al. Holographic optogenetic stimulation of patterned neuronal activity for vision restoration. *Nat Commun* **4,** 1509 (2013). https://doi.org/10.1038/ncomms2500
[58] Pégard, N.C., Mardinly, A.R., Oldenburg, I.A. et al. Three-dimensional scanless holographic optogenetics with temporal focusing (3D-SHOT). *Nat Commun* **8,** 1228 (2017). https://doi.org/10.1038/s41467-017-01031-3
[59] Kim, H., Park, M.Y., Lee, S.D., Lee, W., Chiu, A., and Yoo, S-S. Suppression of EEG visual-evoked potentials in rats through neuromodulatory focused ultrasound *Neuroreport* **26**, 211–5 (2015).