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STANDARDS ROADMAP: NEUROTECHNOLOGIES FOR BRAIN-MACHINE INTERFACING

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TABLE OF CONTENTS

List of Tables

List of Figures

Acronyms

AI	artificial intelligence
ALS	amyotrophic lateral sclerosis
AT	assistive technology
AUC	area under the ROC curve
BOLD	blood-oxygen-level-dependent contrast
BCI	brain-computer interface
BMI	brain-machine interface
CNS	central nervous system
DBS	deep brain stimulation
DTC	direct-to-consumer
ECoG	electrocorticography
EEG	electroencephalography
EMG	electromyography
EOG	electrooculography
ERP	event-related potential
FDA	U.S. Food and Drug Administration
FES	functional electrical stimulation
fMRI	functional magnetic resonance imaging
HFE	human factors engineering
IoT	Internet of Things
LIS	locked-in state
LFP	local field potential
MEG	magnetoencephalogram
MI	motor imagery
MFER	Medical waveform Format Encoding Rules
MRI	magnetic resonance imaging
MUA	multi-unit array
NIRS	near-infrared spectroscopy
NMES	neuromuscular electrical stimulation
OECD	Organization for Economic Cooperation and Development
ROC	receiver operating characteristic curve
RoI	region of interest
SCI	spinal cord injury
SMR	sensorimotor rhythms
SNR	signal-to-noise ratio
SSVEP	steady-state visual evoked potential
tACS	transcranial alternate current stimulation
tDCS	transcranial direct current stimulation
TES	transcranial electrical stimulation
TMS	transcranial magnetic stimulation
tRCS	transcranial random current stimulation
UCD	user-centered design
UE	usability engineering
UWB	ultra-wideband (microwave)
WG	working group
XDF	extensible data format

FOREWORD

WHO WE ARE

The group on Neurotechnologies for Brain-Machine Interfacing is an IEEE Standards Industry Connections activity launched in May 2017. It gathers diverse stakeholders across neurotechnologies, research institutions, industry and government agencies to identify and address gaps in the existing standards in Brain-Machine Interfacing (BMI). It also aims to raise awareness of the importance of standards in the field.

This group is sponsored by the IEEE Society on Engineering in Medicine and Biology (EMBS) Technical Committee on Standards and supported by the IEEE Brain Initiative. IEEE Brain was formed as a new initiative within IEEE Future Directions, with the mission of facilitating cross-disciplinary collaboration and coordination to advance research, standardization, and development of innovative tools and technologies in the field of neuroscience to treat diseases and improve lives.

OBJECTIVES

This document aims at providing an overview of the existing and developing standards in the field of neurotechnologies for brain-machine interfacing. It is mainly focused on systems that provide a closed-loop interaction with artificial devices based on information extracted from measures of the activity in the nervous systems.

In addition to reviewing the most current standardization efforts, this document also reports on the current opinions on the topic as collected by an online survey conducted with members of the community and presents some recommendations on the perceived priorities for standardization.

This document is the outcome of discussions within the group and general public feedback. Despite efforts to comprehensively cover the current situation regarding standardization efforts, we are conscious of the fast-paced development of these technologies and expect this to be a living document that will be enriched by public inputs as new information is available.

AFFILIATED STANDARDIZATION INITIATIVES

In order to fulfill its objectives, the group has organized and participated in multiple activities, special sessions, and workshops in international BMI and neurotechnology-related conferences, spawning a growing suite of complementary standardization working groups, efforts, and forums.

Namely, IEEE Working Group P2731 has recently been established to create a standard for *Unified Terminology for Brain-Computer Interfaces*, while IEEE Working Group P2794 is working to formulate a *Reporting Standard for in vivo Neural Interface Research* (RSNIR), to serve as a framework for the precise, comprehensive reporting of human and animal research throughout the growing ecosystem of neurotechnology. The latter is intended for application to multiple types of reporting, including but not limited to peer-reviewed scientific publication, grant funding applications, research project reports (private or public), and medical device regulatory submissions.

Together, the P2731 and P2794 draft standards are intended to promote continued discovery, technological innovation, and commercial development in the fields of neuroscience and

neurotechnology, by facilitating clear communication across the full spectrum of neurotechnology users and stakeholders, including researchers, engineers, clinicians, end users, regulators, funding agencies, and commercial interests.

Both working groups officially launched in 2019 and are currently active and open to participation from BCI and neurotechnology experts and stakeholders.

STRUCTURE OF THE DOCUMENT

This document is composed of two parts. The first one: "Neurotechnologies for Brain-Machine Interfacing" presents an overview of the standardization efforts and the priorities identified by this group. This part is intended to be self-contained and it is addressed to a wide audience with different levels of knowledge in BMI or related areas but not necessarily experts.

The second part comprises technical appendices providing more detailed information. This part is intended for readers interested in getting a deeper knowledge on the topic.

Considering that BMIs are composed of the integration of multiple technologies, both parts in the document are structured around five main axes. The first three axes cover key technologies for interfacing the user to the BMI system, namely (i) sensing technologies, (ii) feedback mechanisms and (iii) data management. The last two axes focus on (iv) user needs and (v) performance assessment of BMI systems. For each of these axes, we present a brief overview of these sub-topics, existing standards (defined or in progress), as well as recommendations of priority areas for further standard development.

We also report on current perception of standardization in the neurotechnology field as reported in an online survey we conducted among BMI researchers and developers.

STANDARDS ROADMAP: NEUROTECHNOLOGIES FOR BRAIN-MACHINE INTERFACING

1 INTRODUCTION

A brain-machine interface (BMI)[1] is a system that establishes a direct communication channel between the human or animal brain and a computer or an external device. BMIs record or stimulate activity of the central or peripheral nervous system (CNS/PNS) in order to replace [1], restore [2], enhance [3], supplement [4], or improve [5] natural output/input. Thereby the BMI is able to change the ongoing interactions between the CNS and its external or internal environment [6].[2]

BMIs typically measure neural activity through sensors placed inside the brain or body (invasive or implanted technologies) or external sensors (non-invasive technologies). This activity is processed in real-time to extract information about the intentions or states of the subject. Processed information is then used to generate an action or stimulus in the external world that is provided as direct or indirect feedback to the user.

Some BMI examples are communication systems that decode brain responses to external stimuli to select suggested characters (i.e., IEEE P300 spellers) [7]; systems that use electrodes implanted in the cortex to control prosthetic arms or to generate arm movement through PNS stimulation [8], [9].

Research and development in BMI is going through a very exciting period where numerous emergent neurotechnologies are exploiting neural signals for a range of practical applications, both clinical and nonclinical. As research using these technologies continues to improve our understanding of the nervous system, such systems are currently being tested with their intended end users in clinical and real-world environments. This translation from research prototypes to viable clinical or consumer products entails multiple challenges—both technical and commercial.

Most importantly, **BMI systems are the product of integrating multiple technologies. They comprise systems for the acquisition and decoding of neural and biophysical signals to actuators providing sensory, mechanical, and electrical feedback to the user**. Figure 1 illustrates the different processes and elements of the BMI loop. Accordingly, BMIs can be seen as a *system*

[1]These systems are also referred to as brain-computer interfaces (BCI) or brain/neural computer interfaces (BNCI). For sake of clarity the term brain-machine interfacing (BMI) will be used in this document.

[2]Numbers in brackets refer to sources listed in the Reference section.

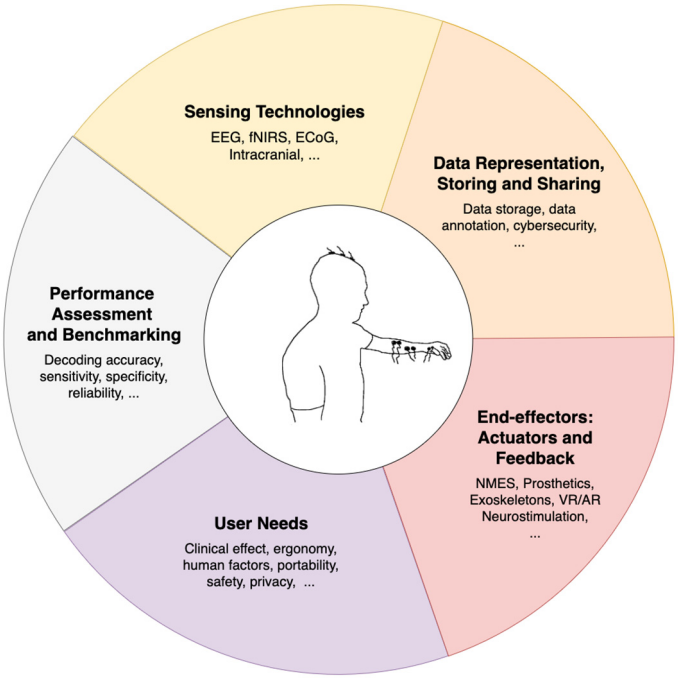

Figure 1—Different axes of analysis of a Brain-Machine Interface system

Figure note—They comprise three technical axes focused on the processing stages of the BMI loop: Sensing, data management and end-effectors, as well as two high-level axes: user needs and performance assessment.

of systems. In fact, the available technologies supporting these sub-systems may be at different stages of maturity, ranging from well-established to emerging approaches. This heterogeneity creates additional challenges for standardization and compliance of BMI systems as a whole.

This document discusses the state of the art in standardization of the different technologies related to BMI and identifies important elements to consider for proper standardization of both clinical and consumer applications. The document is structured around five axes comprising key technological components of the BMI loop (*sensing* technologies, *end-effectors* and *data management*) and high-level characterization of the systems (*user needs* and *performance assessment*).

Context

Currently there is an increase of multi-stakeholder interest on the development of neurotechnologies and BMI. These include large technological companies (e.g., Facebook, Neuralink, Kernel), as well as military and healthcare stakeholders. This is translated in an increase of investment at the international level and high hopes for the societal and economic impact of these technologies.

This increase echoes interest in other novel technologies, in particular artificial intelligence (AI) [10]. Simultaneously, concerns have been raised on the possible ethical, societal and legal consequences, which in turn calls for well-defined principles, standards, and regulations for these developments. As a result, multiple guidelines have been recently released which include the IEEE guidelines for ethically aligned-Intelligent systems, and the IEEE Brain Neuroethics framework.

Similar initiatives specific to neurotechnology are currently emerging including the Neurorights initiative at Columbia University for advocating for human rights directives for developing neurotechnologies and the OECD working paper and recommendation on "Principles for responsible development of neurotechnology enterprises" [11] (see below).

Last but not least, BMI standardization should also consider regulatory frameworks for technology-based systems (both clinical and consumer oriented) in fields like AI, IoT, and cybersecurity. A particular challenge in this aspect is the disparity in regulatory approaches across the world. Noticeably, EU regulation on medical devices is currently approaching the end of the transition period after a legislation change introduced in 2017.

Standards for neurotechnologies

The proliferation of bio-sensing modalities, end effectors, applications, and the diversity of prospective user populations have created the need for a more interoperable ecosystem of neurotechnologies.

Furthermore, the possibility of deploying and commercializing BMI based solutions with human users requires researchers, manufacturers, and regulatory agencies to ensure these devices comply with well-defined criteria for their safety and effectiveness.

These factors generate an increased interest in development of appropriate standards for BMI systems and related neurotechnologies. However, given the novelty of some of the BMI-related technologies, there can also be some reluctance to undertake standardization methods given the multiple unknowns.

Development of standards that balance the potential benefits BMI systems can bring to society and the inherent uncertainty of multiple development options, is not trivial. It is thus important to acknowledge that some of these options are still at an emerging developmental stage and may not yet be mature enough to be standardized.

Hence, **development of standards requires all stakeholders to join efforts to identify priority areas that most require standardization (see Table 2), and to devise incentives and mechanisms for adopting these standards early on at the development process, without hindering timely deployment of new technology-based solutions.**

This process should consider existing tensions that arise in the development of BMI systems (see Table 1). These include balancing the need for clear development and safety guidelines and the inevitable *unknown-unknowns* brought by novel ideas. Other tensions include the differences in development cycles and regulation of consumer versus clinical applications—the importance of data sharing versus the protection of personal data.

State of the art in standardization

The level of standardization of BMI related technologies is diverse. It ranges from topics where there are a solid number of established standards for safety and performance evaluation, while other aspects of development seldom have such standards. Even in cases of existing standards, these typically cover the specific role of that technology (e.g., sensor characteristics, packaging, and safety) but do not cover how it integrates and effects safety and performance of an entire BMI system.

Table 1—Existing tensions in BMI research and development

Safety, reliability		fast innovation financial sustainability
open research		IP protection
clinical regulation	Vs	consumer regulation
public interest		private interest
national/regional approaches		intercultural differences

Currently, **sensing and actuation technologies can be considered to have a high level of standardization**. It is worthy to note that these standards are mainly focused on safety aspects of those technologies. Detailed discussion of the level of standardization of sensing and actuation technology is presented in Appendices II and III, respectively.

In turn, **there are several standards related to data management** covering aspects such as cybersecurity and data representation in medical applications (c.f. Appendix IV). Currently, there is a strong movement towards the development of community-driven recommendations for storing, annotating, and sharing of neural data. The increasing interest for data sharing and scientific reproducibility, championed by international brain initiatives and societies[3,4,5] has driven the development of these recommendations, although they often take the form of guidelines or recommended practices and not as a formal standard.

In contrast, system-level aspects of BMI such as **user needs and performance assessment are not yet the subject of established standards**. Although there are existing standards regarding human factors and usability, they are not widely applied by the BMI research and development community. These axes are further detailed in Appendices V and VI.

Remarkably, recent advances in the field and the prospect of commercialization of both clinical and consumer-oriented applications have motivated multiple efforts to develop guidelines and standards. An important milestone is the release of the FDA draft guideline on implanted brain-computer interfaces in spring 2019 [12].[6] Here, the agency recognizes both the need of developing guidelines and the fact that there are many unknown aspects. Hence, this document is defined as a *leap-frog guideline* that addresses a technology in development and it is subject to change as more information becomes available.

Another relevant effort is the release of the aforementioned OECD working paper on responsible innovation in neurotechnology enterprises. Considering the potential economic impact of

[3] US Brain Initiative

[4] EU-funded Human Brain Project

[5] BrainMaps project

[6] FDA ID: FDA-2014-N-1130-0004

neurotechnologies, this paper discusses approaches that may help to prevent or mitigate some potential risks these technologies may bring. In this respect, OECD highlights the importance of multiple types of governance—including soft-law, good practices, self-regulation and standards—for responsible development of emerging technologies. As such, it is important to recognize that these different approaches are complementary means to guide development of technologies at different levels of maturity.

Recommendations

BMI standardization is a topic that elicits tensions between the need for clear development and safety guidelines required for efficient commercialization and the fact that some of these technologies have not yet reached a high level of maturity. Therefore, we propose the following recommendations:

- There is a need to **promote better education about the positive effects of standardization** and the benefits that developers and innovators may obtain when engaging in the development and definition of standards.
- **Efforts should be invested on educating the community on how standards are developed** to leverage the expressed interest and promote community engagement in the standardization process.
- **Safety, security and privacy appear as top priorities for standardization**. Existing principles, standards, and regulatory guidelines on relevant technologies can be a starting point for BMI specific standards on this issue.
- **There is a clear lack of standards and agreed practices for the terminology used to specify BMI systems, as well as for assessing performance and benchmarking in relevant working conditions**. Consequent efforts should be devoted to redress this situation.
- **Existing trends of to improve scientific reproducibility and open science can be leveraged to establish and consolidate standards for data sharing and reporting on neurotechnology developments.**
- Development of consumer-oriented BMIs can be a driving force to improve the current technology towards more affordable sensing and actuation devices. It also can become a source of valuable data to improve current decoding models. The benefits could efficiently spillover to clinical applications if these devices comply with some of the quality standards required by medical devices. Hence, **the community should consider the possibility of defining complementary standards that scale-up from consumer to clinical applications**. Under this approach, standards for neurotech consumer products will be more accessible, allowing the fast development required for commercial viability, without compromising on their efficacy. Gradually, more stringent standards could be adopted or developed in order to respond to the requirements of clinical applications.
- Implementation of BMI systems may require integration of complementary technologies like artificial intelligence, robotics, internet of things, or VR/AR headsets. The interoperability, including functionality, safety and cybersecurity, has been identified as a standardization priority. **It would be important to encourage the implication of BMI researchers in the development of standards and regulations of these complementary technologies**.
- As any emerging technology, there are many uncertainties about the development of BMI systems. Hence, standardization and regulation should be flexible and agile to react

efficiently to changes brought by new evidence. Therefore**, it is important to envision flexible and consistent governance mechanisms ranging from community-agreed good practices, soft law, standards, and regulation. This may be achieved through implementation of strategies such as regulatory sandboxes** [7] **and regular update of community guidelines and standards**. One example of the latter is the aforementioned FDA draft guideline on implanted BMIs.

- **BMI-specific standards should be aligned with emerging frameworks to address ethical, legal, and societal implications of emerging technologies**. Current initiatives on ethically-aligned design can be an important asset for development of new standards.

The next sections and the appendices present a more detailed explanation and discussion of the standardization level of these technologies.

[7] A regulatory sandbox is a well-defined space where developers can test innovative solutions in live conditions in a relaxed, monitored, regulatory environment.

Table 2—Summary of current state of standardization and priorities for the considered axes

	Standardization level	Background	Priorities
Sensor Technology	High	Established standards for electromagnetic safety, biocompatibility	Interoperability
End effectors	High	Electrical/Mechanical safety Standard for lexicon for prosthetics Ongoing development on wearable robotics	Unified terminology Communication across devices and processes Standards to specify and measure performance of systems relying on shared control
Data Management	Medium/Low	Cybersecurity standards in non-BMI applications Community driven standards EEG consumer devices	Cybersecurity/Privacy Interoperability between data management platforms Data annotation (in real life situation), Definition of meta data and closed-loop data
User Needs	Low	Existing standards for human factors but seldom integrated in BMI design Medical design device control	User requirement and needs of healthy and less severely affected patients User needs (beyond direct user, e.g., caregivers, family) Benchmarking of user needs fulfilling
Performance Assessment	Low	Community driven approaches, focused on neural decoding performance Benchmarking of individual BMI sub-components	Closed-loop evaluation Integration of evaluation of human factors Benchmarking of task-based performance and assessment of clinical use

Public perception on BMI standardization

Besides assessing the existing standards and efforts related to neurotechnologies, we also set out to identify the community perceptions on standardization. For this purpose, we conducted an online survey that took place between the months of June and August 2018. It was launched at the Asilomar International BCI meeting in Pacific Grove, California, and later promoted through messages to the group members, the mailing list of the International BCI Society, and through social media (Twitter, LinkedIn, and Facebook) by the IEEE Brain initiative and by individual members. A total of 83 people responded to the survey. Participants had different levels of experience, a majority of them working in academia (n=60; ~72.3%). Hence, the findings reported here may not capture accurately the perception of non-academic members of the BMI community.

About two thirds of all participants hold a PhD degree and less than 10% were at an undergraduate level. A detailed analysis of the survey is available in Appendix I.

Standardization priorities

Participants ranked the level of priority for standards on different topics in Figure 2. The **safety** of neurotechnologies was consistently ranked as a very high priority for standardization. This was followed by **data privacy and cybersecurity**, **data ownership**, and to a lesser extent, **neuroethics**. These concerns are consistent with reports on other emerging technologies like artificial intelligence, data-based applications, wearable devices, and internet of things (IoT).

Next, high levels of priority were assigned to technical aspects linked to **data representation and sharing**, **terminology and specifications**, as well as **performance evaluation and benchmarking**.

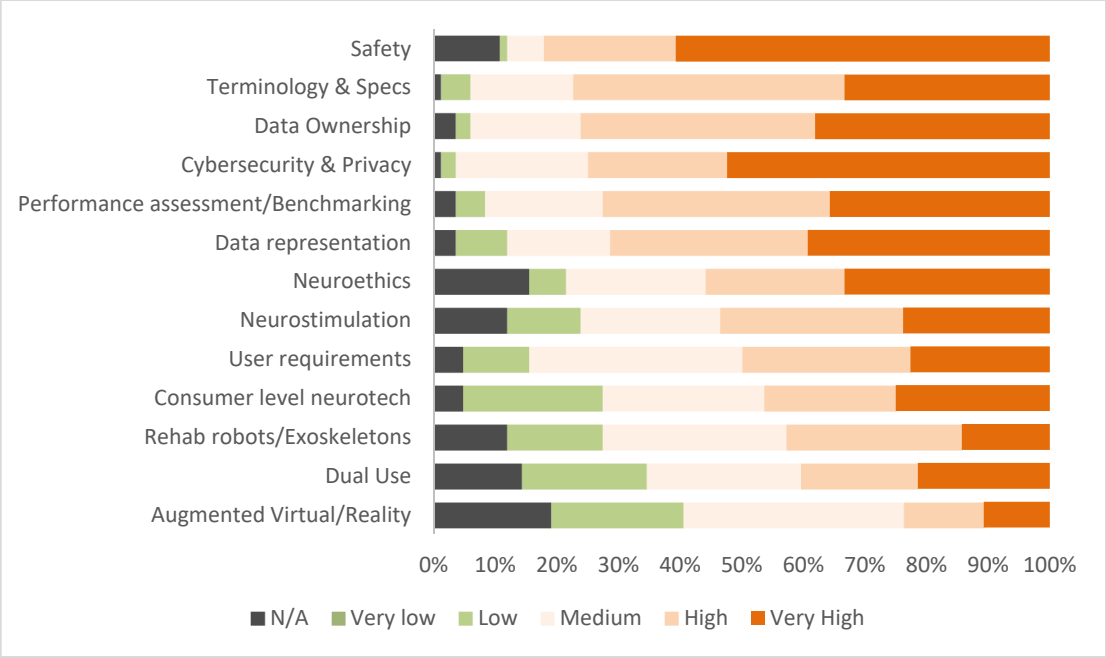

Figure 2—Level of priority as rated by survey participants (N=83)

Respondents pointed out the need for better ways to compare the performance and efficacy of systems and devices developed by different groups, as well as the importance of being able to use data collected at multiple sites or by different individuals in order to validate and improve the technologies.

Standardization of BCI end-effectors like rehabilitation robotics and AR/VR are perceived as having mid-priority. One possible explanation may be that the BMI community considers development of these standards as specific to these technologies and involvement from BMI developers may be minor. A different pattern was observed for **neurostimulation techniques that were also reported as being a high priority**. The lack of long-term information on the safety of these techniques as well as the existence of an active DIY community interested in this type of technology may explain its ranking as a high priority.

BMI Standards: Promoter or hindrance to development?

Most participants considered standards a promoter for development of new technology. It should be taken into account that most respondents worked in academia or industrial research environments. Interestingly, about **half of the participants say they are motivated in the development of standards, even though a majority manifested a lack of familiarity with standards development processes**.

Responses show **strong support to the position that consumer-oriented applications should follow similar standards as clinical applications**. This is important to provide consumer protection, as well as addresses the likely scenario of consumer-oriented systems being used in wellness or health-oriented applications. Either as off-label use or as part of interventions aiming to have clinical impact (e.g., telemedicine, virtual-reality supported motor rehabilitation). However, it cannot be concluded that clinical and consumer standards should be exactly the same. Members of this group have proposed to consider the possibility of **defining complementary standards that scale-up from consumer to clinical applications**. Within this family of standards, those devoted to consumer products will be more accessible, allowing fast development required for commercial viability, without compromising on their efficacy.

Conclusions

Participants in the survey expressed a marked interest for standardization for neurotechnologies and motivation to get engaged in their development. Nonetheless, a generalized lack of knowledge of the very same development process was also reported.

Responses showed a positive perception of standards as a promoter of better technologies, although they also reflect the perception that both standards and regulation may slow down development and innovation. In a related manner, participants believed that consumer and clinically oriented applications should have similar standards. This is seen as a mean to avoid new technologies to misinterpret or misuse neurotechnologies. However, instead of compelling both cases to follow exactly the same level of standards, it is proposed to have complementary standards where consumer-oriented standards are a subset of the clinical ones.

Avoiding negative impacts of neurotechnologies seem to guide the perceived priorities for standardization. Hence, aspects of safety, data privacy and ownership, and cybersecurity rank as the highest priorities. Similarly, neurostimulation techniques was also reported a major priority. Careful consideration of the ethical aspects of the use of these techniques should be followed in the development of standards. IEEE Guidelines for ethically aligned design and the IEEE Brain

Neuroethics framework can be useful tools in this process. These topics are followed by standards on data sharing, specification, and benchmarking.

Sensor Technology[8]

Background

In a broad sense, the goal BMI is to extract information from neurons in living organisms and convey such information to artificial devices.

There is a wide range of technologies available to perform these measurements. Currently, most non-invasive BMI systems rely on electroencephalography (EEG). In the case of invasive BMIs, implanted electrodes, either on the surface of the brain or by intra-cortical electrode arrays, are the most common techniques. Among the other possible techniques, we can find approaches at different levels of technological maturity, from emerging approaches only tested in-vitro or in animal models, to techniques already tested and validated in humans. Figure 3 illustrates some currently available measurement techniques, while their advantages and disadvantages are summarized in Table 3.

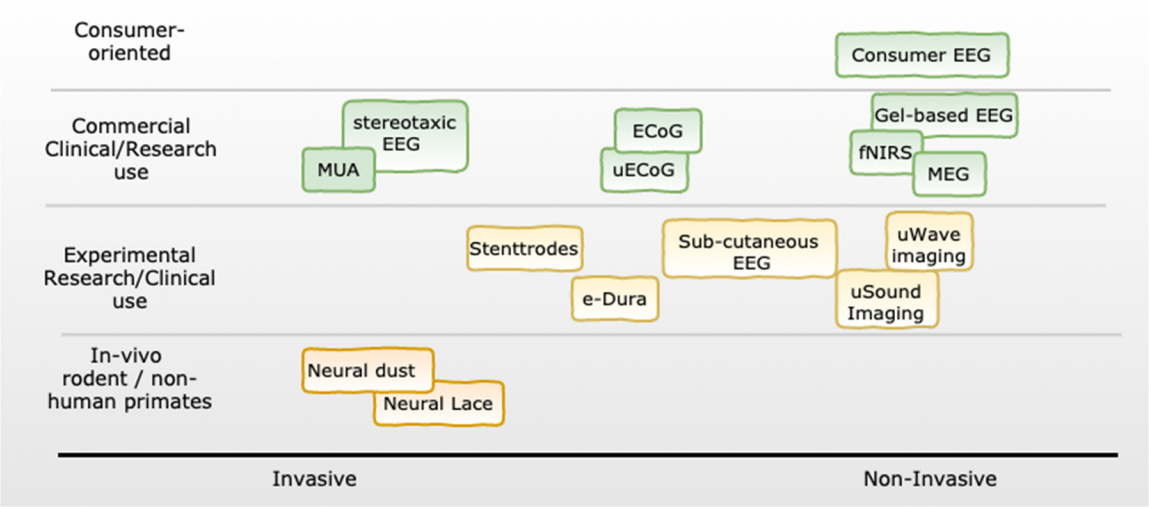

Figure 3—Current and emerging sensing technologies [13], [14]

Intra-cortical Multi-unit array electrodes (MUA)[15], *Stereotaxic EEG, Neural dust* [16], *Neural lace* [17], *Stenttrode* [18], *E-dura* [19] , *Electrocorticography (ECoG)* [20], *micro-ECoG* [21], [22], *functional near-Infrared spectroscopy (fNIRS), microwave imaging*[23], *ultrasound imaging, subcutaneous electroencephalography (EEG)* [24], *Magnetoencephalography (MEG)* [25], *Gel-based EEG* [24], *Dry electrode/Consumer oriented EEG headsets* [26]

Besides development of more performance and reliable measurement approaches, there is an increasing interest on developing technologies that allow long-term recordings and use in real-life environments. In consequence, features such as power autonomy, wireless data transmission, usability, and ergonomic aspects start to play an important role in the new generation of sensing technologies.

Among the different BMI technological axes covered in this document, sensing technologies are arguably the field with the highest level of standardization. Given the use of the most established techniques in clinical applications, several standards have been established based on their

[8]Detailed information and discussions on standards related to sensing technologies can be found in Appendix II.

performance and safety. However, even with these standards, there is a large variable space that can differ among sensors such as: size, shape, and material of the sensor. Table 4 reports the main standards in this respect.

Given their novelty, other emerging sensing techniques are not yet subject to standardization. Nonetheless, it is worth mentioning the IEEE P2725.1 Working Group on Standard for Microwave Structural, Vascular, or Functional Medical Imaging Device Safety. This group has taken a proactive approach to define a safety standard in parallel to the development of clinically-oriented applications of the recording technique.

Recommendations

An important gap in standardization of sensing techniques concerns the **interoperability**. Neuroimaging and BMI research and development uses more and more frequently multiple modalities, also combining neural recordings with other physiological signals and data fusion from multiple sources. Proper analysis of the data recorded by these multi-modal setups require reliable time synchronization across data streams.

This issue imposes particular challenges as these systems are likely to combine on equipment from different manufacturers. However, **there is no established standard for time synchronization among different systems, since the interfaces and ports to those systems vary**.

Furthermore, development of consumer-oriented devices for measuring brain-activity can also have an impact in health-oriented and clinical applications. Given the market size, consumer-oriented neurotechnologies have the possibility of producing more affordable sensing alternatives. This advantage can spill over to clinical applications **as long as consumer graded sensors comply with safety and performance standards that are consistent with the requirements of clinical devices**.

Table 3—Sensing modalities for brain-machine interfacing

	Techniques	ADVANTAGES	DISADVANTAGES
Non-Invasive	EEG MEG fNIRS	• No skull transgression • No neural tissue damage • Can be setup outside clinical environments • Low risk	• Lower spatial resolution • Lesser precision • Slower operation (fNIRS) • May require bulky headsets or wired BMI connections
Invasive (current)	ECoG Intra-cortical electrodes	• Higher resolution • Greater precision • Faster operation	• Neural tissue damage • Neural tissue inflammation • Neural tissue displacement • Implanted probes/electronics displacement • Implantation accuracy • Flexible implant difficulties • Incompatible with high temperatures
	Techniques	• **INTENDED ADVANTAGES**	• **POTENTIAL DISADVANTAGES**
Invasive (emerging and novel)	Optogenetics Stentrodes Neural Dust Neural Lace	• Includes Invasive (current) advantages • Reduced/eliminated neural tissue inflammation • Less rejection by neural tissue • Significantly smaller dimensions • Wireless • Battery-free • Mesh introduction via injection • Stable localization • Long-term (potentially lifelong) operation • Integration with electrocorticography and optogenetic technologies	• In some cases, no evaluation in humans • Lack of data on chronic recordings • Neuromorphic implant may merge with neural tissue, presenting potential difficulties if implant removal/replacement is required

End-Effectors: Actuators and feedback devices[9]

Background

The crux of BMI systems is to use the information extracted from the nervous system to provide interaction mechanisms throughout artificial devices (henceforth referred to as end-effectors). These include prostheses, exoskeletons, video games or feedback mechanisms. Therefore, development of BMI systems requires the integration of actuation mechanisms based on a variety of technologies. Importantly, often actuation technologies are conceived for purposes and working conditions that are not limited to BMI applications and include both consumer-oriented and clinical applications. The end effector systems described herein are divided into seven main categories: (1) upper limb exoskeletons, (2) lower limb exoskeletons, (3) upper limb prostheses, (4) lower limb prostheses, (5) powered wheelchairs, (6) neurostimulation devices, and (7) virtual/augmented reality (VR/AR).

There are considerable efforts on developing **upper limb** and **lower limb exoskeletons**. These systems have been largely intended as assistive or rehabilitative tools for individuals with motor limitations. These systems use different control and actuation strategies and have been used as end-effectors on BMI systems using both invasive and non-invasive approaches. The FDA categorizes exoskeletons as Class II medical devices with special controls, and has cleared four exoskeleton devices for marketing in the U.S.

Similarly, extensive research has been done on **BMI controlled prosthetic devices**. The uses of myoelectric control for upper-limb prosthetics is a popular strategy in commercial products. In contrast, most BMI studies on upper-limb prosthetics control use an external robotic arm instead of a prosthetic device as an end effector. This type of setup has been used to test control of arm movements, different types of grasping and hand shaping using EEG, ECoG, and microelectrode arrays. In contrast, the development of powered lower-limb prosthetics is a rather recent endeavor, with no studies yet showing BMI control of these devices.

Another type of BMI controlled mobility assistance device are **powered wheelchairs**. Multiple research prototypes of non-invasive approaches to wheelchair control have been reported in literature, but currently there is no available product on the market.

The use of **neurostimulation** is becoming an important focus of research and development of BMI systems. There are multiple techniques that are used in this context. **Functional electrical stimulation** (FES) is a technique that delivers electrical stimulation to peripheral nerves to elicit muscle contraction. This allows motor intentions decoded in neural signals to be used to generate upper or lower limb movement patterns for assistive purposes. The use of BMI triggered FES has also been proposed as a potential tool to promote neural plasticity in motor rehabilitation after stroke.

Transcranial stimulation is another technique of interest. Magnetic or electrical stimulation applied non-invasively is used to generate electromagnetic fields, which modulate activity of neural populations.

Conversely, implanted electrodes can also be used to provide focused electrical stimulation. Intracranial cortical stimulation is used to alleviate chronic pain. Another use is **deep brain stimulation (DBS)**, where electrodes are implanted in deep areas in the brain to treat symptoms of Parkinson's disease. Lately, the use of this technique has been extended to other pathologies.

[9]Detailed information and discussions on standards related to end-effectors can be found in Appendix III.

These stimulation approaches are typically used in open-loop; hence they are not technically a BMI. Nonetheless, the use of closed-loop control of the DBS patterns have been proposed as a mean to reduce secondary effects and extend the stimulator battery life.

Intra-cortical micro-stimulation has been used to elicit neural activity that can be interpreted by the user as sensory information. It has thus been proposed as a technique that, linked with prosthetic devices, can be used to provide tactile sensations and proprioceptive information about the prosthesis state.

Similar to sensing technologies, **end-effectors intended for clinical applications have a rather mature level of standardization**. This is summarized in Table 5.

The International Society for Prosthetics and Orthotics has developed a comprehensive lexicon for Standard Terminology on the topic. Exoskeletons and wearable robotics are included in the scope of an ISO standard currently in development under the ISO/TC 299 robotics working group (IEC/DIS 80601-2-78). Moreover, the IEEE Robotics and Automation Society is developing a standard for wearable robotics focused on non-medical applications.

Complementarily, two EU-funded projects are currently aimed at developing benchmarking frameworks for robotics[10] and building a multidisciplinary community that focuses on responsible research and innovation paradigms for interactive robotics.[11]

Recommendations

Despite the existence of a standard terminology for prosthetics and orthotics, **some terms related to the BMI control of these devices lack a clear definition**. Some of these terms include the distinction between active and passive systems, the definition of continuous and state-control. Similarly, there is no standard taxonomy of the motor functions that a given device may perform.

Interconnection between BMI sensing and processing modules and the end-effector requires the definition of standards for data communication. Ideally, this communication standard may allow 'plug-and-play' settings where a BMI system can interchange functionally similar end-effectors without need for redesign and expect the same behavior. These standards should consider both commands to send to the end-effector and feedback information about its state to other BMI sub-modules.

Real life applications require the BMI system to allow execution of complex tasks in unstructured environments. In order to achieve this, BMI designers often use a **shared control** where actuators are endowed with some autonomous capabilities that allow it to assist and even override human control in certain situations [27]. The shared control design and architecture has strong impact on the features and performance of the BMI since it balances information and commands from different sources. **Standardization of shared control strategies and architectures will be important to improve the reliability and safety of the BMI as a system of systems**.

[10] http://eurobench2020.eu/

[11] http://inbots.eu/

Data representation, storing, and sharing[12]

Background

Data representation, storage, and sharing has gained significance in view of the need for efficient representation and interoperability. As an evolving domain, initial efforts in the BMI domain focused on the design and development of processing pipelines, while the need for standardization in data representation and storage was a secondary concern. However, present day requirements for efficient storage and secure interoperability have led to an increasing emphasis on approaches for data storage and sharing.

There have been diverse efforts by research groups worldwide to define data formats for various biosignals. This document discusses existing data formats and frameworks, as well as prevalent and upcoming initiatives by research groups, standardization agencies, and other entities for both time-series and imaging-based biosignal modalities. These include formats such as EDF/GDF, BCI2000, XDF, MFER, sdeeg; standards such as IEEE P1752/P7002/11073, ISO 22077-1:2015, ANSI/CTA-2057/2058/2059/2061; frameworks such as LSL, OpenBCI, OpenViBE; and groups such as NeuroData without Borders, NIF, Brain-CODE, BIDS, INCF, among others (see Table 6 for a summary). While we see that multiple initiatives and adoption levels exist, the need for streamlining efforts towards evolving a comprehensive set of standards for data representation, storage, and sharing is a challenge and needs to be addressed on priority.

Recommendations

Efficient storage and secure interoperability, for both closed and open loop paradigms, has emerged as the need of the hour as far as standardization initiatives for data storage and sharing for BMIs are concerned. There is a growing need for global adoption of representation formats that support efficient compression schemes so that storage (or memory) footprint of biosignals can be optimized. The primary nature of biosignals being high-dimensional time-series (or image sequences) mandate the need for data formats optimizing storage complexity. These formats also need to take into account the representation of intra/inter subject/trial annotations, confidential user information, experimental/acquisition modality and interoperability scope and compliance.

Further, aspects related to data security are also important when sensitive data is shared across heterogeneous systems. These systems range across clinical data management systems, healthcare data aggregators, consumer-grade systems for diverse applications (clinical and commercial), as well as ubiquitous platforms including mobile devices and Internet of Things (IoT) devices. Evolving computing paradigms such as cloud, fog, and edge computing present challenging vulnerabilities as far as data security and integrity are concerned. As such, efficient encryption mechanisms need to be in-built into data representation schemes.

There is also a growing need for device manufacturers (of biosignal acquisition devices) to adopt common data representation formats so that data exchange could be facilitated. Interoperability is notably dependent on compliance by data-generating sources; hence, devices play a key role in its realization. The review of existing data standards in this document strongly evidences the need for participating entities (including industry and research players) to work in coordination

[12] Detailed information and discussions on standards related to data representation, storing, and management can be found in Appendix IV.

to define and adopt data formats that facilitate the key objectives of storage efficiency and secure interoperability.

User Needs[13]

Background

Accounting for user needs and usability in the development of medical devices is a clear regulatory mandate, identified by ISO 14971 (Risk Management for Medical Devices) as a requisite for identifying and mitigating user-related hazards, and by the U.S. federal Quality System Regulation for medical devices (21 CFR 820.30) as a primary source of input to the Design Controls process (Subpart C, §820.30). However, the responsibility for defining and implementing the human factors engineering/usability engineering (HFE/UE) processes necessary to meet these regulatory requirements currently falls to device developers, resulting in significant variability in the fulfillment of user needs by final products. Moreover, because a large portion of early stage neurotechnology research is conducted in the academic domain, prior to explicit plans for commercial development, the **HFE/UE aspects of system design are often underdeveloped during the early stages of technology transfer, further elevating the burden and the difficultly for neurotech developers to obtain regulatory approval and commercialize.**

In the medical and commercial sectors alike, it is now widely recognized that organizational implementation of HFE/UE and user-centered design (UCD) processes yield significant down-stream benefits, including higher user satisfaction, better product adoption, reduced net development costs (by avoiding unanticipated design revisions in later stages of development), and early insight regarding future products, features, and markets. However, these net benefits typically incur substantial up-front development costs that many small and medium enterprises find burdensome (if not prohibitive) in the face of overall high development cost and market pressures to take the fastest possible path to market.

These early-stage development costs result largely from the need for neurotech developers to define and execute their own HFE/UE/UCD processes, in a decision space with an overall lack of consensus regarding precise usability metrics and evaluation methodologies. Thus, standardizing the identification of primary user needs and the corresponding application of HFE/UE/UCD processes to specific classes and use cases of neurotechnology holds immense potential to minimize these development costs while maximizing the effectiveness and benefit of HFE/UE/UCD to manufacturers.

Overview and Synthesis of User Needs Standardization Landscape

To date, frameworks and processes for the identification and fulfillment of user needs in the development of interactive and computer-based technologies have been well outlined in the HFE/UE/UCD process, as articulated by several standards, including ISO 9241-210 (Human-Centered Design for Interactive Systems). Significantly, this process—and the associated disciplines of HFE/UE from which it is derived—have been investigated, described, and codified at length at multiple key levels of public documentation, including scientific and clinical literature, international consensus standards, and best-practice guidance by medical device regulatory bodies. A complete summary of HFE/UE/UCD standards pertinent to user needs for neurotechnology is given in Table 7. Among these standards, IEC 62366 (Usability Engineering for

[13]Detailed information and discussions on standards related to user needs can be found in Appendix V.

Medical Devices), ISO 9241-210 (Human-Centered Design Processes for Interactive Systems), and ANSI/AAMI HE75 (Human Factors Engineering—Design of Medical Devices) form the central pillars of the HFE/UE/UCD processes.

The core principles of HFE/UE/UCD established and shared among these standards include the early and iterative involvement of users in the product design and development process, consideration of the specific abilities, needs, and desires of individual users and user populations, and the heavy dependence of usability on the context(s) and objective(s) of intended system use (i.e., use cases). Among the key definitions, ISO 9241 defines usability as "the extent to which a […] product […] can be used by specified users to achieve specified goals with effectiveness, efficiency, and satisfaction in a specified context of use." By this definition, BMI system usability—and thus, its ability to fulfill user needs—depends critically on both the characteristics/abilities of the user and the functions/uses for which the BMI is designed and applied.

In addition to standardized HFE/UE/UCD processes and their application to medical devices, there are a number of additional standards for product development processes and usability evaluation in the domain of software and information technology. Namely, the ISO/IEC 25000 series defines *System and Software Quality Requirements and Evaluation (SQuARE)*, with specific user needs-related standards including ISO/IEC 25022 (Measurement of quality in use) and ISO/IEC 25066 (Common industry Format for Usability—Evaluation Reports). Insofar as all BMI systems include software, and most include some form of computer-based user interface, many of these standards and their provisions are applicable to neurotechnology usability as well, though current literature contains no reference to the specific application of these software standards to BMI systems. Additional usability-related standards that may likewise be applicable or informative but have yet to be rigorously applied for BMI usability include ISO/IEC 29138 (User Interface Accessibility), ISO 14915 (Software ergonomics for multimedia interfaces), and ISO 20282 (Usability of Consumer Products).

In addition to the user requirements described above, the usability of BMI systems will depend on other technical aspects that need to be addressed and standardized. Some of these aspects include the need for portability or wearability. Generating the possible need for wireless devices or cloud-based data processing services. Correspondingly, power management of these devices is another requirement that needs consideration. Last but not least, practical BMI applications should provide the possibility of being used independently by the user for long periods of time. Generating further requirements for their acceptability for long-duration use, durability and, field serviceability.

Recommendations

While the principles and processes defined by the aforementioned standards are thorough, clearly articulated, and applicable to a wide range of human-machine interfacing technologies (both medical and non-medical), none of them are specific to neurotechnology, much less to particular BMI modalities or use cases. In particular, they provide no guidance regarding the key tasks/functions for which to design or the methodologies/metrics with which evaluate BMI technologies in terms of usability and fulfillment of user needs. Nor do they define any specific BMI use cases, classes or characteristics of BMI users. **Given that the concept of usability and its evaluation are predicated on a clear and precise definition of the intended users and use cases, the lack of standards in this area presents a significant 'standardization gap.**'

In this vein, underlying the usability evaluation (benchmarking) gap in particular—and necessary in order to address it—is the lack of unified, standard terminology concerning a host of usability-

related concepts, including the definition of the term "user need" itself. Likewise, the above standards contain no prescriptive process for the identification and articulation of user needs, nor prioritization among them. As an illustrative example, BMI clinical researchers have noted that "ease of use" can mean different things to different users, and that in the absence of clear definitions, users may conflate related concepts such as ease of use, cognitive load, ease of learning, reliability, and the ease/burden of system maintenance. A final and important limitation is that **existing standards focus primarily on usability through the lens of product safety and the mitigation of user-related risks, not on the totality of usability, including all aspects of effectiveness, efficiency, and user satisfaction**. Fortunately, a number of these gaps have been addressed to a significant degree at the level of clinical research and scientific literature, as summarized below.

User Needs Research, Publication, and Current Practices

Below the level of international consensus standards, there has been a substantive amount of clinical and scientific research and publication in the area of BMI user needs, to identify and characterize BMI users and use cases, to specify user needs particular to leading user classes/use cases, and to apply HFE/UE/UCD standards to neurotechnology.

In the latter category, a large research consortium, funded by the recent European Commission ICT Program Projects TOBI (2008-'13) and BackHome (2012-'15) and led by Kübler and colleagues, has extensively adapted and implemented the detailed UCD process specified by ISO 9241-210 for a range of high-need clinical BMI users (including those with ALS, stroke, and SCI) and use cases (including communication and brain painting), and found the UCD process to be applicable and informative to BMI system development [28].

With respect to evaluation of BMI usability, a 2017 systematic review of BMI literature by Choi and colleagues [29] identified a consolidated set of seven tasks used for BCI usability evaluation, 21 performance measures, and 40 subjective measures of usability used in current practice, as well as several barriers to standardization. Notably, from this diversity of existing BMI assessment measures, authors proposed a consolidated usability framework based around the three core concepts of effectiveness, efficiency, and user satisfaction, in alignment with the ISO 9241-210 definition.

As an additional framework, the EU Brain/Neural Computer Interaction (BNCI) Horizon 2020 project, based on the previous work of Wolpaw and colleagues [6], has agreed upon six *application scenarios* (i.e.,classes of use cases) with respect to natural central nervous system (CNS) input: *replace*, *restore*, *enhance*, *supplement*, *improve*, and *research tool*. Loosely speaking, these use cases lie along a spectrum of user impairment, from replacing CNS function for severely and permanently impaired users (e.g., locked-in or high-level SCI), to restoring/supplementing/enhancing CNS function for moderately impaired users and/or those with recovery potential, to improving CNS function for healthy users, as well as for researching all states of healthy and pathological CNS function.

Naturally, the greatest attention to date has been given to the most severely impaired users, who represent those with the highest clinical need. In this vein, as the output of a clinically-focused BMI development workshop held by the FDA in 2014, a broad coalition of BMI researchers and neural rehab clinicians defined five primary classes of needs for prospective BMI users: functional independence, comfortable integration of BMI systems with the body, ease of use, comfort and convenience in prolonged use, and, critically, the need for BMI system makers to remain active, for ongoing technical support and maintenance [6]. Beyond these direct user needs, the

workshop also identified a series of necessary elements of the BMI development process to better address user needs, necessary elements of BMI-related clinical practice with respect to user education and support, critical areas for further user-related research, and necessary regulatory innovation.

Between the application of the HFE/UE/UCD process to BMI technology and the identification of user needs by multiple parallel research projects and initiatives, the field of BMI user needs-related research appears largely convergent, with broad alignment and common reference to existing standards regarding the definition of usability and the core principles and processes for incorporating it into BMI system development—most notably, the early and continuing involvement of users in an iterative design process. In sum, this convergence provides fertile ground for existing BMI user needs research and frameworks to be formalized into neurotechnology-specific standards.

Priorities and Recommendations for further standardization

In recent years, there has been a growing recognition in the field of BMI research that in order to properly fulfill user needs at scale, neurotechnology must not only account effectively for user needs in the design process, but must also achieve successful clinical translation, commercial development, regulatory approval, and long-term market viability. Indeed, the translation from laboratory prototype to regulatory-approved medical device is where a majority of innovative and promising technologies fail. Thus, **as a guiding principle, standardization efforts should prioritize and target the aspects of neurotechnology design and development that will have the greatest impact in facilitating clinical validation and commercialization, by providing detailed user needs frameworks that reduce the total time and resources required while maintaining or improving the rigor of device R&D efforts.**

To this end, the systematic evaluation and inclusion of user needs in the technology development and validation process, though not without substantive operational requirements and corresponding costs, offers the strong potential for net cost reduction and quality improvement in the product life cycle management of neurotechnologies. In order to maximize the effectiveness and minimize the cost of such efforts, the neurotechnologies for BMI group recommends the development of standard methods and metrics that can serve in the identification/specification of user needs and the evaluation of their fulfillment across the full range of neurotechnological maturity, from laboratory prototypes to investigational devices to commercial and clinical devices. Accordingly, such measures should be recognized by scientific, clinical, and regulatory communities alike. In this way, data gathered in the earliest investigational stages of technology development can serve both the near-term publication and research funding interests of academic and not-for-profit researchers, as well as the subsequent commercialization interests of technology owners and developers.

In the domain of user needs, a fundamental challenge to be addressed is that current standards do not provide (or foresee) easily implementable prescriptions regarding the identification or fulfillment of user needs—rather, they define high-level HFE/UE/UCD *frameworks* and *processes* that are fundamentally iterative and must be customized to specific technologies and use cases, thus warranting dedicated organizational infrastructure and personnel. Moreover, there has emerged a clear consensus between both standards and the BMI community that active, frequent user input in the design and development process is indispensable. Thus, the focus of standardization should not be to obviate user involvement completely through the precise and comprehensive definition of user needs, but rather to establish a hierarchical family of standards based on a unified classification of neurotechnology modalities, users, and use cases. Within this

family, a parent standard may define high-level user needs generalizable across multiple classes of technology and use case, while modular sub-standards provide increasingly prescriptive methodologies and measures for refining and evaluating these needs for specific user types and use cases.

To realize this vision, the consolidation and standardization of usability measures within the three areas of effectiveness, efficiency, and user satisfaction is essential and should be prioritized. As well, given the natural and inevitable diversity of neurotech users in terms of pathology, ability, and personal priorities, standard instruments and surveys should be developed for classifying individual users, identifying their priorities, and choosing the most appropriate BMI systems and configurations accordingly. To enable this customizability, modularity and interoperability of neurotechnology will play an important role. Furthermore, within the classification of users, it will be important to account for multiple (often parallel) domains of users, including primary end-users (patients), and a variety of secondary users, including clinicians, researchers, and caretakers.

At the practical level, a major barrier to the inclusion of user input in the neurotech design process is often access to sizeable and representative samples of prospective users. Here, neurological patient associations, advocacy groups, and large clinical centers of excellence can be very helpful by seeking and maintaining active collaborations with both the BMI research and commercial development projects—and by publicizing opportunities for participation in such research to their patients and members, along with ample education and support regarding the associated risks and benefits of participation. Indeed, while the outreach and inclusion of users remains critical, so too does adherence to carefully designed and ethics committee/institutional review board (IRB)-approved research protocols, wherever applicable.

Finally, **at the clinical implementation level, clear clinical guidelines must be developed regarding the appropriate selection and customization of neurotech systems for individual patients/users**, including clear clinical indications and contra-indications for certain BMI system/types, implantation and fitting procedures, as well as user training and support.

Performance Assessment and Benchmarking[14]

Background

The assessment of BMIs should comprise evaluation of both the hardware and software assessments. The hardware includes acquisition devices, actuators, and form factors. Software primarily relates to interface (and stimulation types) and machine learning techniques.

Although there is a plethora of methods to evaluate these individual components, there is no formal way to effectively assess the impact of performance of these individual elements to the overall performance of the BMI system.

Performance evaluation of individual hardware components follows standard practices described in the sections devoted to sensors and end-effectors. In addition to that, some researchers have proposed the use of specific batteries of tests to assess the quality of the recorded neural signal. These tests may range from electrical measures (e.g., impedance measures), to calibration based on user tasks (e.g., measuring EEG with eyes open and closed, evoked neural responses, among others) to evaluate SNR and neural baseline activity.

Furthermore, although BMI performance should be measured in real-life closed-loop conditions, assessments and benchmarking of its components are typically performed in simulation and off-line analysis. This is often motivated by the difficulty to evaluate the contribution of inter-subject differences in performance variations. Unfortunately, it has been consistently shown **that offline evaluation of performance is a poor predictor of closed-loop performance.**

Research literature on the evaluation of BMI systems have been disproportionally focused on the (offline) assessment of the decoding algorithms. A wide variety of metrics from machine learning have been used to evaluate the decoding performance including: Accuracy, Precision, Recall/Sensitivity, F1-score, or Confusion matrices. Additional metrics derived from information theory have also been used to assess performance of continuous decoding of brain signals. Cross-validation schemes and its influence on this performance measures are often disregarded in scientific literature. Currently, **there is no consensus on which validation schemes and performance metrics should be used to assess and compare performance of BMI decoders**.

The accuracy of the BCI decoding algorithm is not the only factor to take into account. Indeed, many BMI setups do not take individual decoding outputs directly to perform the intended actions. For instance, non-invasive typewriting applications based on the P300 evoked response typically average of the EEG responses of multiple stimulus presentations before inferring which is the intended character to be written. In turn, BMI systems relying in shared-control approach combine the decoded output with other information streams and computations made by the controlled effector to decide the action to be performed. In consequence**, there is a need to define performance metrics based on the domain of the task to be achieved**. For instance, in terms of the number of correctly written characters in the case of typewriting systems or the number of correctly executed actions by an exoskeleton or a powered wheelchair.

[14]Detailed information and discussions on standards related to performance assessment and benchmarking can be found in Appendix VI.

Last but not least, successful development and adoption of BMI systems requires designers to take into account factors of ergonomics and usability of the interface. Elements discussed in the section devoted to user needs have yet to be considered in the performance evaluation.

Recommendations

Actual performance of a BMI system is a composite of multiple factors involving its different hardware and software components. There is a well-established number of methods to evaluate the performance of these systems individually. However, there is no agreed standards on which are the most suitable validation scheme and metrics to be used to assess and benchmark them. A clear priority is thus to develop standards and protocols for measuring BMI performance. Importantly, these procedures and metrics should go beyond separate evaluation of each sub-component and allow assessment of the BMI as a whole during closed-loop operation.

In consequence, assessment should consider the effect the human-in-the-loop has on the system performance. Human factors should be included, in combination with quantitative metrics of the technical components. Importantly, the development of a standardized way to report BMI systems and their performance evaluation is key to allow researches of different groups to perform a fair comparison of multiple design approaches to solve the same task. Two recent IEEE Standards Association projects are aimed at addressing this issue—IEEE P2731: Draft Standard for a Unified Terminology for Brain-Computer Interfaces and IEEE P2794: Draft Standard for Reporting of In Vivo Neural Interface Research.

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2 APPENDICES

Appendix I—Public survey on standards for neurotechnologies

This survey was developed to gather information on the perceptions on the topic of standards for neurotechnologies. It was implemented as a Google forms link and took place between the months of June and August 2018. It was launched at the occasion of the International BCI meeting in Asilomar in California, and later promoted via messages to the members of the group on Neurotechnologies for Brain-Machine Interfacing, the International BCI Society, as well as the social media feeds (Twitter, LinkedIn and Facebook) of the IEEE Brain initiative, and group members. The entire content of the survey is available in the following link.

Demographics

A total of 83 people responded to the survey; with a majority of participants (n=60; ~72.3%) working in academia. About two thirds of all participants hold a PhD degree and less than 10% were at an undergraduate level.

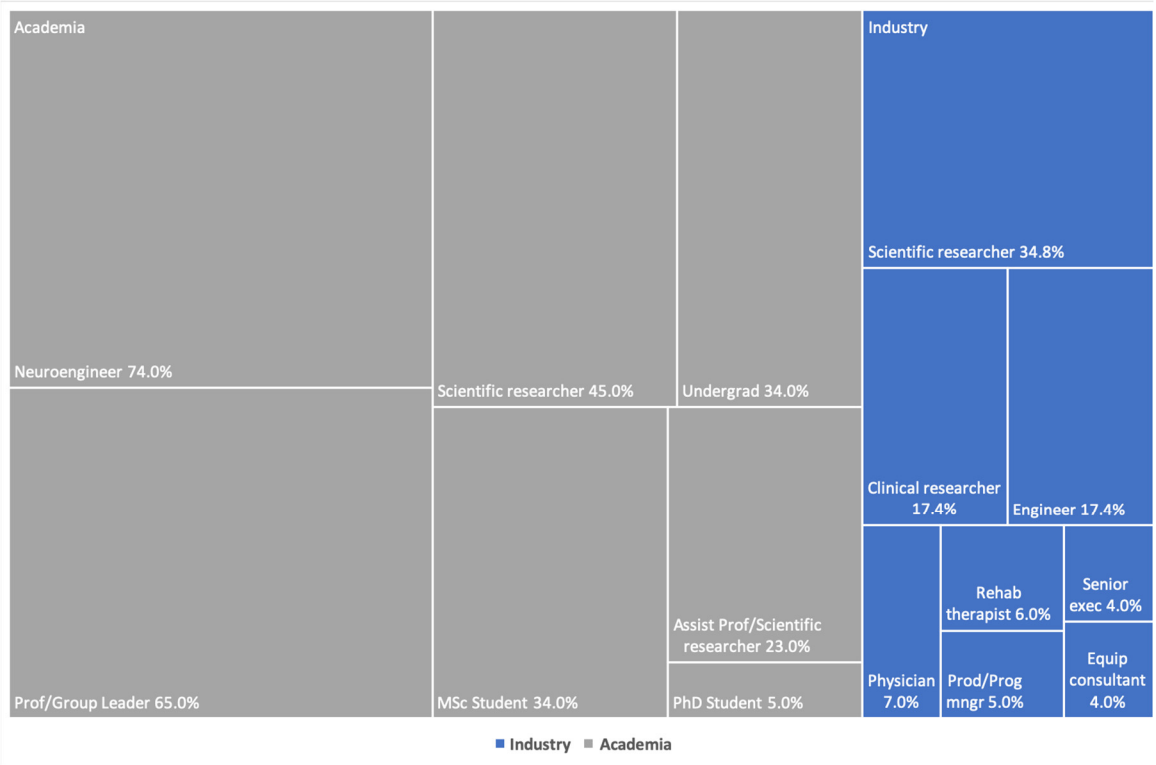

Figure 4—Demography of survey participants—Current occupation

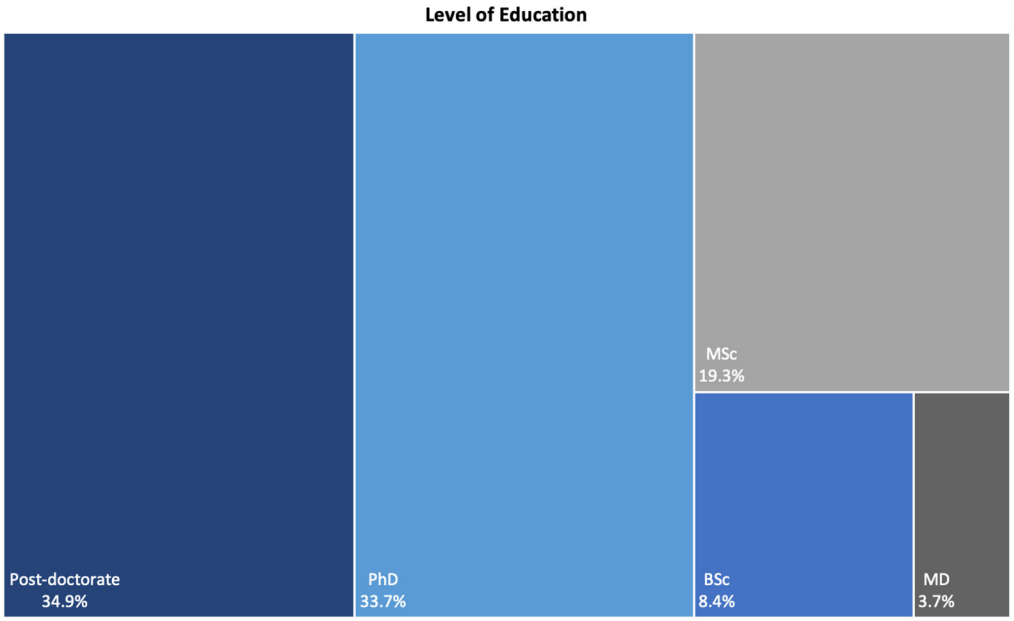

Figure 5—Level of education of participants in the survey

Standards as a promoter or hindrance to the development of new technologies

The majority of participants considered standards as a promoter for development of new technologies, and less than 15% of them considered them as a potential hindrance. This position may be influenced by the fact that most participants in the survey came from academia. Additional comments offer a more nuanced perspective where respondents link the need of standards to the level of maturity of the technology (some claiming that it is "too early for standards"), while others prone for standardization at the high level and not only for implementation details.

Interestingly, the association between standards and regulation seems to drive the conception that the formers are an obstacle for innovation. Hence, **it is important to promote better education about the positive effects of standardization and the benefits that developers and innovators may obtain when engaging in the development and definition of standards.**

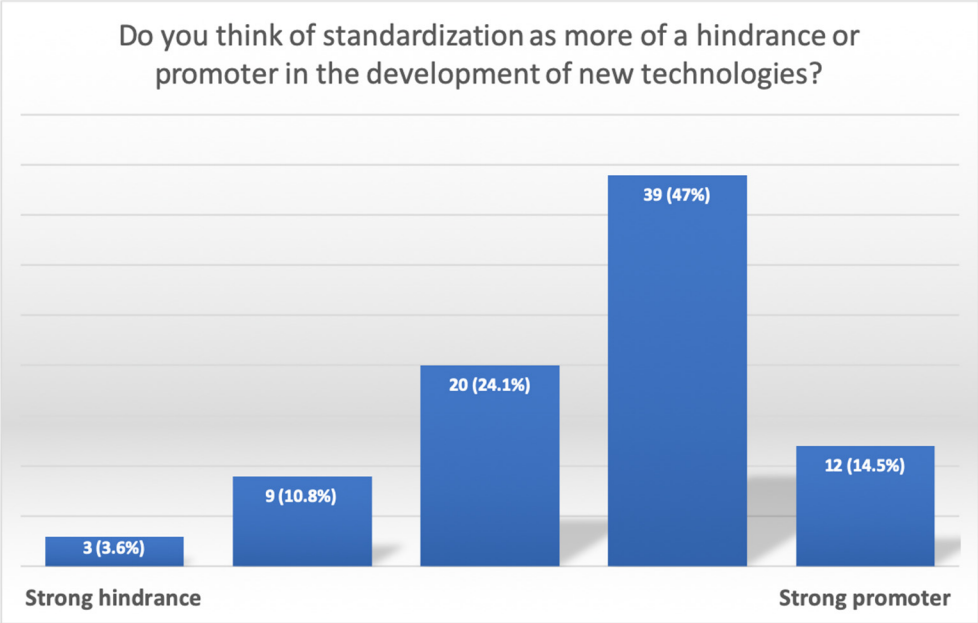

Figure 6—Standardization as a promoter or hindrance to neurotechnology development

Participants' comments on standards as a promoter of hindrance to technology development

"Standardization has a strong potential to promote innovation, but the realization of this potential may be hindered by a widespread (mis)perception among academic and industrial innovators that standardization (by association with regulation) inhibits innovation."

"I think standardization can come in place when new technologies are being used clinically whereas it might be of hindrance in the development of those technologies."

"Strongly depends on an area, maturity of a technology, etc."

*"Standardization has a strong potential to promote technological development, *provided that the core capabilities of those technologies are first established.* Additionally, there is a widespread association between standardization and regulation as hindrances to innovation that should be addressed and nullified by our messaging efforts."*

"Probably too early for standards."

"It depends, if you standardize too early it can slow improvements. If you do it when the technology is mature enough it can speed things up."

"Tradeoff can work both ways."

"In terms of what?"

"Would make approaches to interaction more comparable and guidelines could be developed."

"Facilitates cross-technology development."

"Depends what level of design is standardized. I feel standardizing high levels could be helpful to abstract away underlying implementation."

Motivation and familiarity regarding standards development

Half of participants expressed being motivated to participate in the development of standards. However, most of them also manifested a lack of familiarity with the process of developing a standard**. It is therefore utterly important to devote efforts on better instructing the community on how standards are developed to leverage the expressed interest and promote higher community engagement towards proper standardization of emerging technologies.** IEEE can exploit its technical expertise on standards and educational resources to actively lead such a process.

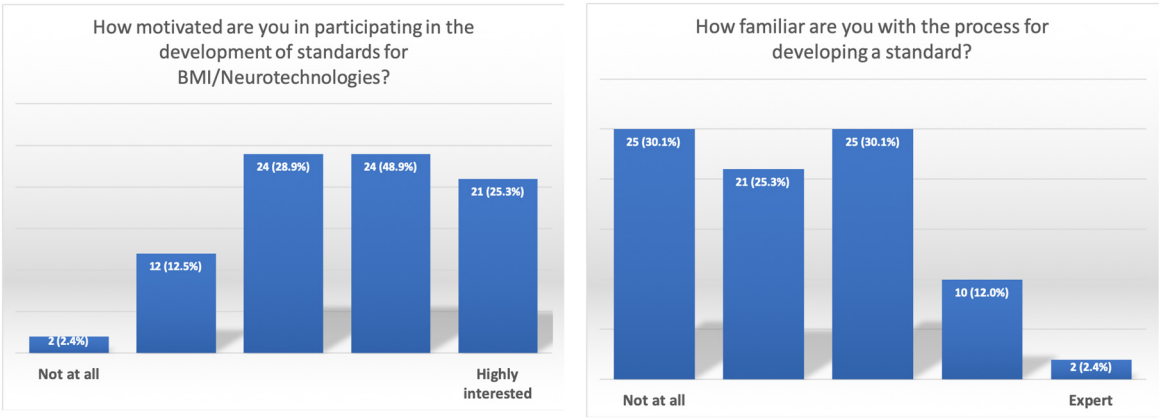

Figure 7—Motivation and familiarity vis-à-vis standards development

Clinical and consumer-oriented applications

Responses show **strong support to the position that consumer-oriented applications should follow similar standards as clinical applications**. While recognizing that applications in these two fields face different scenarios and their use may lead to radically different consequences, it was nonetheless perceived that consumer-level neurotechnologies may not be working as expected by their users and mislead their users.

However, it cannot be concluded that standards in the two cases should be exactly the same. It has been proposed to **consider the possibility of defining complementary standards that scale-up from consumer to clinical applications. Within these families of standards, those devoted to consumer products will be more accessible, allowing fast development required for commercial viability, without compromising on their efficacy. Gradually, standards will become more stringent to respond to the requirements of clinical applications**.

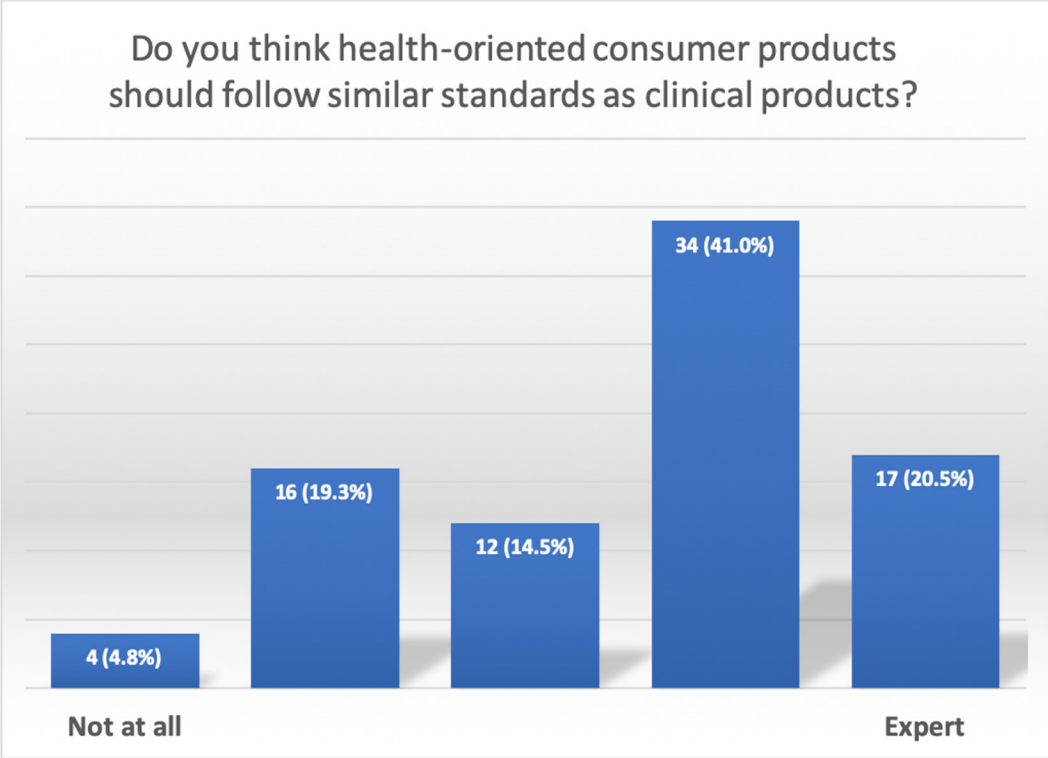

Figure 8—Perception on whether clinical and consumer-oriented and clinical applications should follow similar standards

Participants' comments on standards for clinical and consumer-oriented applications

"The adherence of consumer products to the same family of standards as clinical products will facilitate the development of better, more user-friendly clinical products, and will also enable the makers of consumer products to more easily expand their markets to include clinical 'indications for use.' However, it is also important that the more stringent tiers of standards/requirements for clinical products be clearly differentiated from non-clinical consumer product requirements, so as to avoid aversion by makers of consumer products in adhering to the same family of standards."

"I recommend structuring standards in such a way that health-oriented consumer products are subject to standards that represent a subset of standards for clinical neurotechnologies, with clinical technologies naturally carrying an additional layer of standardization. This way, the work done to commercialize consumer devices is applicable towards the application (and regulatory approval) of those devices for clinical indications as well."

"There are a lot of health oriented products that are not working and people believe in it. It is frustrating when people try to use such products instead of going to physicians."

"In the case of new BCI technologies yes. Even if 1% caused damage that is way too much. But if a standard / technique is developed and given approval new variations should not need to go through the whole approval process again."

"There are policies for this already."

Priorities

The reported levels of priority for standardization are illustrated in Figure 2.

Given the nature of neurotechnologies and their clear link to clinical applications and welfare, it is not surprising that the '*safety*' of neurotechnologies was reported as having a very high priority for standardization. This was followed by '*data privacy and cybersecurity,*' '*data ownership,*' and to a lesser extent 'neuroethics.' Such concerns can be linked to the potential damage these technologies can directly and indirectly cause to their users and, in the case of security concerns, is complemented by similar issues concerning other emerging technologies like social media, internet of things (IoT) and wearable devices.

Another set of topics pointed as standardization priorities are more related to the development of the technology. Aspects like '*data representation and sharing,*' '*terminology and specifications,*' as well as '*performance evaluation and benchmarking.*' These issues denote a need for better ways to compare the performance and efficacy of systems and devices developed by different groups, as well as the importance of being able to use data collected at multiple sites or by different individuals in order to validate and improve the technologies.

Standardization of BCI end-effectors like '*rehabilitation robotics*' and '*AR/VR*' are perceived as having mid-priority. One possible explanation may be that survey participants considered the development of these standards as specific to these technologies and the involvement from the BMI community on this process may be minor. A different pattern was observed for '*neurostimulation'* techniques that were also reported as being a high priority. As mentioned previously, the potential damage these techniques may produce as well as the existence of an active DIY community interested in this type of technologies may explain why it is considered a priority.

Open Question: Which other topics do you consider to be priorities for standardization?

- *Electro-mechanical (hardware) connections between different neurotech system modules*
- *Standard BNCI Model: all comes from a well-defined functional BNCI model.*
- *Signal quality*
- *Safety, performance and benchmarking*
- *Performance standards, terminology is key to communicating and evaluating BMI devices for an application. Communication is key to a communal development.*
- *Sensor interconnectability*
- *Purchase of some components*

- *Neural interface (e.g., implant) hardware; surgical implantation techniques; ... and *maybe* neural signal*
- *Processing techniques*
- *Cost*
- *Neurohacking*
- *Number of participants to include in a study.*
- *Biomaterial safety evaluation*
- *That BCI adopt existing standards. To ensure plug and play capability*
- *Data representation and evaluation standards*
- *communication protocols between BCI software and applications*
- *Preprocessing pipeline*
- *experimental protocol design and user experience evaluation*

Other comments and feedback

"It's important to develop a standardization framework that applies (and is amenable) to all stages of neurotech research and development, with requirements and guidelines specific to appropriate stages development. In terms of messaging, standardization should be promoted as a means of both improving the ease (lowering the barrier to entry) of developing new neurotech, improving the quality of resulting products, and lowering the corresponding regulatory burden."

"Focus on what BMI and neurotechnologies are unique and not reuse what has been used in speech/image processing, computer vision, and HCI."

"The technology and devices themselves and even how they work can't follow strict standards without hindering development."

"Sometimes requiring standards on new products would not allow them to come to market."

"Another key question for our group to address is how to create a system/framework of incentives for researchers and innovators to adhere to standards beginning early in the development process."

"I am not sure if this is relevant but a concern of mine is monopolies. If Facebook or Openwater patent their new optical/holography techniques and don't allow anyone to use them they essentially own the whole BCI market. They should have their own product, even get a commission[sic] for every product sold using their technology but there should not be a sole manufacturer of software or hardware."

"In the context of Neuroethics 'standards' could mean different things. Standards in terms of ethical aspects below which no BMI/BCI should fall and standards of reporting and communicating."

"Standards will be more needed once there is a real useful BCI application that cannot find any alternative, and brain waves are not used for marketing only."

Conclusions

Participants in the survey expressed a marked interest for standardization for neurotechnologies and motivation to get engaged in their development. Nonetheless, a generalized lack of knowledge of the very same development process was also reported.

Responses showed a positive perception of standards as a promoter of better technologies, although they also reflect the perception that both standards and regulation may slow down development and innovation. In a related manner, participants believed that consumer and clinically oriented applications should have similar standards. This is seen as a mean to avoid new technologies to misinterpret or misuse neurotechnologies. However, instead of compelling both cases to follow exactly the same level of standards, it is proposed to have complementary standards where consumer-oriented standards are a subset of the clinical ones.

Avoiding negative impacts of neurotechnologies seem to guide the perceived priorities for standardization. Hence, aspects of safety, data privacy and ownership, and cybersecurity rank as the highest priorities. Similarly, neurostimulation techniques were also reported as a major priority. These topics are followed by standards on data sharing, specification, and benchmarking.

Appendix II—Sensor technology

State of the art in sensor technology

In a broad sense, the goal of brain-machine interfaces (BMI) is to extract information from neurons in living organisms and covey such information to artificial devices to fulfill several functions including consumer-oriented applications, assistive technologies or therapeutically or rehabilitation clinical applications. Most BMI systems currently rely on EEG (for non-invasive applications) and implanted electrodes either on the surface of the brain or by intra-cortical electrode arrays [30]–[33].

Non-Invasive technologies

Electroencephalography (EEG)

The EEG is the recording of brain electrical activity from the scalp. The first human EEG recording was performed by Hans Berger in 1929, an Austrian psychiatrist. The EEG measures the difference in potentials between electrodes generated by ionic currents flowing within neurons of the brain[24], [34]. It is thought that it takes on the order of a million neurons firing in unison, or near unison, to detect an EEG signal with conventional electrodes. The EEG can be recorded with sub-millisecond timing. However, the spatial resolution is around 3.0 cm. Brain-generated activity measured by EEG is typically smaller than co-existing fields generated by muscular activity or external sources. Therefore, signal processing techniques are required to filter out these signal artifacts [35], [36].

Even with poor spatial resolution, EEG is still a standard practice in clinical settings such as diagnosis of epilepsy and for research such as brain-computer interfacing. In recent years, electrodes, signal acquisition hardware, and signal processing software have undergone major improvements allowing new and improved applications of EEG. For instance, traditional acquisition systems use gel-based electrodes to improve the SNR of the recorded signal. In order to improve the potential use of this technique in consumer-oriented applications, there is an increased interest in the development of EEG systems based on dry electrodes, as well as wireless, portable systems [26], [37], [38].

Magnetoencephalography (MEG)

This technique utilizes a superconducting quantum interference device (SQUID) that is extremely sensitive to the magnetic disturbances created during neuronal activity [39]. This device can be used to non-invasively detect the magnetic field signals around the scalp (~50–500 ft) that are generated by neural activity. Modern MEG devices typically employ helmet-shaped sensor arrays of more than 300 SQUIDs that are systematically arranged to cover the entire scalp.

Functional near infrared spectroscopy (fNIRS)

fNIRS is a noninvasive brain monitoring technology that relies on optical techniques to detect changes of cortical hemodynamic responses to human perceptual, cognitive, and motor functioning [40]. It is a recent neuroimaging tool that is still evolving fast. Ultra-portable wearable and wireless fNIRS sensors are already breaking the limitations of traditional neuroimaging approaches that imposed limitations for experimental protocols, data collection settings, and task conditions at the expense of ecological validity. Through Neuroergonomics [41], [42] and similar initiatives, that advocate measuring the brain function in natural environments, fNIRS is

emerging as one of the sensors that can meet the challenge. Future fNIRS systems are expected to emphasis two types: i) ultraportable, wearable sensors that will allow continuous and ubiquitous measurements throughout our daily life. ii) high-density and feature-rich systems that measure whole head but comes as with large hardware and systems.

Another key advantage of fNIRS is its ease of integration with other modalities such as EEG. Multimodal measurements, specifically fNIRS+EEG, becoming a widespread approach as it has been shown to provide more information than any of the modalities individually. Similarly, fNIRS shows great promise for integration with neurostimulation modalities[43]. Since fNIRS relies on optical properties, there's no systemic interference from tDCS and TMS and can be used simultaneously to investigate the effect of tDCS and TMS on the cortex before, during and after stimulation continuously [44].

Invasive Technologies

Intracranial EEG: Stereotactical EEG, Electrocorticography (ECoG).

Stereotactical EEG (sEEG) is an approach to perform intracranial recordings where electrodes are surgically implanted in deep areas of the brain using a minimally invasive procedures [45], [46]. This technique is used in a clinical setting for long-term monitoring and seizure onset localization in patients with epilepsy [46], [47].

ECoG is an intracranial measurement technique in which electrical activity is recorded directly from the surface of the cerebral cortex [20], [33], and as such, is sometimes described as *semi-invasive*. ECoG utilizes a flexible, closely spaced subdural/epidural grid or strip of electrodes to record the cortical activity. Compared to non-invasive techniques, it avoids signal-distortion introduced by the skull and intermediate tissue. Hence, ECoG has both high temporal (millisecond scale) and high spatial (millimeter scale) resolution. The spatial resolution of the recorded electric field depends on the characteristics and density of the electrode array/grid [13]—and although a semi-invasive technique, ECoG has the advantage of spatial resolution significantly higher than that of EEG (tenths of millimeters versus centimeters, respectively), thereby allowing a more precise identification of the cortical location being measured [48].

Microfabricated Electrocorticography *(micro-ECoG or μECoG)* is an ECoG advance that achieves greater precision through microscale electrodes, much smaller contact sites, and higher spatial resolution. Moreover, these properties allow μECoG to enhance ECoG's suitability for neural interfaces and Brain-Machine and Brain-Computer Interfaces [20], [49].

Intracortical Electrodes

Microwire, micromachined, and polymer-based intracortical electrodes (i.e., implantable neural interfaces) have faced a range of issues, including biocompatible materials, ideal probe shapes, insertion methods, and—most challenging—the long-term reliability required for chronic use. Despite successful demonstration of BMI systems using these electrodes, their long-term usability is yet to be confirmed. An in-depth review of the literature published in 2017 concluded that "Currently existing materials do not have proper set of mechanical, biological nor electrical properties to match neural tissue, thus creating the need for the hybrid materials that could offer such." [15]

Novel Technologies

Stent-Electrode Recording Array (Stentrode) is a high-fidelity intracranial electrode array for recording and stimulating brain activity that differs from traditional arrays by chronically recording brain activity from within a vein using a passive stent-electrode recording array implanted into a vein through catheter angiography (rather than requiring direct implantation into the brain via open craniotomy, a procedure that can cause tissue inflammation). Current stentrode limitations include delivery wire durability and electrode density. Potential solutions being investigated, respectively, include a wireless signal and power transmission system that is smaller than technology currently available; and smaller electrodes, a wireless system, or custom-designed stent technology [18]. After evaluation in animal models, tests of this technology in humans have just recently started.

Nanotechnologies address multiple aspects of sensors relevant to neurotechnology, including 1) the interest in measuring neural activity with minimal side-effects to the living organism, 2) portability of devices and convergent technologies and 3) the potential to explore, identify, and implement new biological readouts for neural circuitry, synaptic pruning, and other complex neuronal and neurophysiological functions. This has led to numerous efforts to explore reduction in scale and the use of neuroscience and brain mapping nanotools. Nanoscale communication addresses the issue of moving information in an end-to-end fashion from the originating data site, such as a sensor or natural or synthetic organelle, cell or system, to other locations within or outside of the organism with as little impact to the organism as possible. It is a critical link in multiscale events that have bottom up influence. Common terminology, concepts, metrics, and reference models that enable this goal have been standardized in IEEE Std 1906.1-2015 and are being modeled in IEEE P1906.1.1. The implementations covered in the standard are broad and encompass electromagnetic, electrical, and molecular diffusion, cellular-signaling, and quantum effects, salient examples being *bionanoprotonics*, that could function as both neuroprosthetics and artificial neurons by monitoring protonic current flow [50]; and *neurobiohybrid* brain tissue interfaces for neural recording, augmenting brain function with intelligent neuroprostheses, and neural therapies such as *Neural Dust*, an implanted 10–100 µm free-floating, independent battery-free sensor motes that are powered by and communicate via a subcranial wireless ultrasonic backscatter transducer (which features long-range communications that allow neural dust to operate as a BMI with lifelong operational capacity [51]. [15, 16] *Injectable Mesh Electronics*, which comprise neuron-sized ultra-flexible open mesh probes, implanted into the brain by injection via a syringe, that seamlessly interface with neural tissue and have a minimal immune response, thereby eliminating the inflammation and scarring associated with standard neural implants [52], [53], and intraneuronal molecular signaling models, which provide new roadmaps to how intracellular pathways contribute to cognitive neurodegenerative diseases, such as Alzheimer's, which has been directly aligned to IEEE Std 1906.1 as a nanoscale communication system [54]. The standard enables a common understanding for XML/JSON descriptions facilitating online and offline exchange of nanobiological configuration and metrics and eases reproducibility of simulations and experiments. IEEE P1906.1.1 is actively developing a YANG (data modeling language for the definition of data sent over network management protocols) framework implementing concepts and terminology of IEEE Std 1906.1-2015. A draft of the model will be available Q1 2020 at https://github.com/YangModels/yang. The philosophy of the

[15] https://www.darpa.mil/news-events/2016-08-03

[16] https://spectrum.ieee.org/biomedical/devices/4-steps-to-turn-neural-dust-into-a-medical-reality

IEEE 1906.1 standard series has been to directly link nanoscale biological communication systems to digital communications.

Graphene—despite having properties (electrical conductivity, biocompatibility, mechanical strength, and high surface area) favorable to neural tissue engineering—also has negative qualities, including not possessing the ability to stimulate neural stem cell adhesion, proliferation, differentiation and neural regeneration, as well as potential body damage. However, graphene nanocomposites (combinations of graphene with other materials) are excellent at not only neural regeneration, but also stimulating neural stem cell adhesion, proliferation, and differentiation. Recently, researchers reported results of the effects of graphene nanocomposites on neural stem cell differentiation and neural regeneration constructs, discussing a challenging neural condition—Peripheral Nerve Injury (PNI), which causes (among other symptoms) pain, sensory loss, impaired movement, and cold intolerance—as a condition that could possibly benefit from graphene nanocomposite-based treatment. That said, the researchers also stress the need for further research owing to issues such as potential of biodegradation of graphene-based materials, as well as to pathology due to the interaction of graphene nanomaterials and exogenous thermal, optical, and electrical stimulation [55].

Portable Infrared based imaging. OpenWater is a startup developing a wearable cap-like technology that will use infrared light and optoelectronics to measure brain blood flow. Defining it as a low-cost fMRI (functional Magnetic Resonance Imaging) alternative, the device is intended to diagnose not just brain injuries or neurodegenerative diseases, but also cancer, cardiovascular diseases, internal bleeding, mental diseases, and BMI applications.[17]

Microwave-based Brain Imaging. Ultrawideband (UWB) microwave pulses can penetrate the skull and travel into deep brain tissues. It is currently possible to generate customizable pulses, launch them into the cortex in a non-invasive manner, and monitor in real-time the resulting reflection. Microwave brain imaging systems developed jointly by Medfield Diagnostics and Chalmers University of Technology for differentiating hemorrhagic strokes from ischemic strokes [56] are currently undergoing clinical trials [57], while many other organizations are working on improved apparatus and algorithms for microwave brain imaging [58], [59]. Additionally, it is anticipated that functional and vascular cranial imaging prototypes under development [23], [60], [61] will begin human subjects trials by the end of 2020.

Tripolar concentric EEG ring electrodes. A new electrode configuration, the tripolar concentric ring electrodes (TCREs) has been developed to address many of the limitations of EEG by the group of Walt Besio at the University of Rhode Island, USA. The TCRE sensors have been shown to significantly improve the signal-to-noise ratio [1], spatial resolution [2], and temporal frequencies over conventional sensor technology [62]–[64]. TCREs can also be used for transcranial stimulation and is currently being tested on animal models as a potential approach to treat epilepsy (e.g., aborting seizures, real-time seizure and protecting the brain from becoming epileptic) [65]–[67].

[17] https://www.openwater.cc/

Level of standardization

Existing standards

Technical standard IEC 60601 for medical equipment covering basic safety and performance requirements for medical equipment, including EEG and ECG. Other relevant standards include the IEEE 21451 series of sensors standards and IEEE Std 2700-2017 on sensor performance parameter definition. Some standards relevant for sensing technologies are listed in Table 4.

FDA regulates electrodes as a Class II device 21 CFR 882.1320: A cutaneous electrode is an electrode that is applied directly to a patient's skin either to record physiological signals (e.g., the electroencephalogram) or to apply electrical stimulation. Cortical and depth electrodes are regulated by 21 CFR 882.1310 and 21 CFR 882.1330, respectively.

In a clear example of proactive efforts for standardization, the recently established IEEE P2725.1 Working Group on Standard for Microwave Structural, Vascular, or Functional Medical Imaging Device Safety, has the goal of attempting to ensure that this emerging modality develops in a manner in which research subjects, patients and commercial users are not unduly subject to safety risks during deployment and commercial realization.

Synthesis: Priority topics and recommendations

An important gap in standardization is related to **interoperability**. Neuroimaging research that records using multiple modalities, such as combined fNIRS and EEG, or neurostimulation and neuroimaging, or studies that record from multiple subjects' brains at the same time require precise time synchronization for accurate analysis. There is no standard for time synchronization among different systems, since the interfaces and ports to those systems vary. Furthermore, it is often cumbersome to come up with a custom solution to each new research setup based on the devices involved.

Table 4—Standards related to sensing technologies

STANDARD	DESCRIPTION
MEDICAL EQUIPMENT (IEC 60601)	
IEC 60601-1-2	Medical electrical equipment—Part 1-2: General requirements for basic safety and essential performance—Collateral Standard: Electromagnetic disturbances—Requirements and tests
IEC 60601-1-6	Medical electrical equipment—Part 1-6: General requirements for basic safety and essential performance—Collateral standard: Usability
IEC 60601-1-8	Medical electrical equipment—Part 1-8: General requirements for basic safety and essential performance—Collateral Standard: General requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems
IEC 60601-1-10	Medical electrical equipment—Part 1-10: General requirements for basic safety and essential performance—Collateral Standard: Requirements for the development of physiologic closed-loop controllers
IEC 60601-2-26	Medical electrical equipment—Part 2-26: Particular requirements for the basic safety and essential performance of electroencephalographs
IEC 60601-2-33	Medical electrical equipment—Part 2-33: Particular requirements for the basic safety and essential performance of magnetic resonance equipment for medical diagnosis
IEC 60601-2-40	Medical electrical equipment—Part 2-40: Particular requirements for the basic safety and essential performance of electromyographs and evoked response equipment
IEEE 21451 series of sensors standards (including some joint with ISO)	
IEEE 21451-001-2017	IEEE Recommended Practice for Signal Treatment Applied to Smart Transducers
Other sensor-related IEEE standards and projects	
IEEE Std 2700-2017	IEEE Standard for Sensor Performance Parameter Definitions
IEEE P2510	Draft Standard for Establishing Quality of Data Sensor Parameters in the Internet of Things Environment
Emerging imaging technologies	
IEEE P1906.1	Draft Standard Data Model for Nanoscale Communication Systems
IEEE P2725.1	Draft Standard for Microwave Structural, Vascular or Functional Medical Imaging Device Safety
Other	
IEEE Std 802.15.6	IEEE Standard for Short-Range, Low Power, and Highly Reliable Wireless Communication In, On and Around the Human Body [68]
GUIDELINES, GOOD PRACTICES AND OTHER REFERENCES	
C. C. Duncan *et al.*, "Event-related potentials in clinical research: Guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400.," *Clin Neurophysiol*, vol. 120, pp. 1883–1908, Sep. 2009. [69] R. Hari et al., "IFCN-endorsed practical guidelines for clinical magnetoencephalography (MEG)," Clin. Neurophysiol., vol. 129, no. 8, pp. 1720–1747, 2018. [70] T. W. Picton *et al.*, "Guidelines for using human event-related potentials to study cognition: Recording standards and publication criteria," *Psychophysiology*, vol. 37, no. 2, pp. 127–152, Mar. 2000. [71]	

Appendix III—End-effectors: Actuators and feedback devices

State of the art in end-effectors

The control and manipulation of various types of end effectors by BMI systems is the target of many commercial and academic research projects. End effector systems are often used for replacing or improving lost functionality, often resulting from physical or neurological injury. End effector systems encompass a broad range of devices and functions, including devices/systems that assume both anthropomorphic and non-anthropomorphic forms. The end effector systems described herein are divided into seven main categories: (1) upper limb exoskeletons, (2) lower limb exoskeletons, (3) upper limb prostheses, (4) lower limb prostheses, (5) powered wheelchairs, (6) neurostimulation devices, and (7) virtual/augmented reality (VR/AR). All of the systems considered are active in the sense that the BMI control invokes some form of actuation[18] that assists the user through some intended action. Among these devices, some have been previously interfaced with BMIs, whereas others have only been controlled through other forms of neural signaling. Here we discuss the most current standardization efforts within each subcategory; provide references to relevant existing standards; and summarize gaps in existing standards.

Exoskeletons, rehabilitation and assistive robotic platforms

Upper limb exoskeletons

A considerable number of upper limb exoskeletons (at least 80) have been developed both commercially and in academic or private research institutions, primarily for rehabilitation of any combination of the shoulder, elbow, and wrist joints after injury (most commonly stroke). Two comprehensive reviews of these systems were published in 2017 [72], [73], with Stewart's review focusing specifically on hybrid exoskeletons, i.e.,those which are used in conjunction with Functional Electrical Stimulation (FES) to facilitate muscle contraction. These exoskeletons utilize a variety of control schemes (e.g., force control, impedance control, PID control) and can also serve as an end effector for brain-computer interfaces by taking advantage of neurological signals as inputs with EMG [74] and less commonly EEG [75], [76], while no known studies exist for invasively-acquired signals such as ECoG or microelectrode arrays.[19]

Lower limb exoskeletons

Lower-limb, powered robotic devices have emerged as assistive and rehabilitative tools for individuals with motor limitations. These devices have enabled individuals to walk and exercise in previously unavailable ways [77]. The devices fall under two categories: wearable joint actuators [78] or devices fixed to a platform (e.g., treadmill-based or paddle-based devices) [79]. Powered orthoses induce motion to one or more paralyzed lower limb joints using external power, usually via electric, pneumatic or hydraulic actuators [80]. More recently, exoskeleton devices have emerged as aids for over-ground, bipedal ambulation. The U.S. Food and Drug Administration (FDA) has recognized exoskeletons as Class II medical devices with special controls, and has cleared four exoskeleton devices for marketing in the U.S.: ReWalk Personal (ReWalk Robotics, Israel), Indego (Parker Hannifin, USA), Ekso GT (Ekso Bionics, USA), and Medical HAL (Cyberdyne, Japan). Recently, Rupal et al. conducted a thorough review of existing exoskeletons, including medical and non-medical assistive devices [81]. Several studies have reviewed existing lower limb exoskeletons in a clinical context, evaluating the outcomes, effectiveness, possible benefits [82]–[85] and potential risks, and adverse events [86]. Although the design forms of

[18]Mechanical in the case of robotic platforms; digital in the case of VR/AR; electrical for FES.

[19]Some studies have used robotic devices to provide weight support for BMI controlled FES systems but in these cases, there was no direct control of the robotic device [197].

these orthoses and exoskeletons differ greatly, at core they are all powered robotic devices that assist walking for medically related purposes.

Upper limb prosthetic devices

Powered upper limb prostheses allow amputees to regain arm and hand functionality required for numerous daily activities. Advancements in the robotics and control allow for finer manipulation of the individual joints required for highly dexterous hand movements. The following literature reviews and compares prosthetic arms and hands on the market and under development [87]–[89], while specific references to these devices are also provided.[20] Myoelectric control is a popular advanced control scheme for upper limb devices that allows for intuitive control through the activations of residual muscles. Advanced surgical techniques, such as targeted muscle reinnervation [90], [91], allowed for the development of myoelectric devices, with amputations occurring as high as the shoulder. Few studies have been published that explored the real-time control of robotic arms and hands through BMI. Surgically implanted microelectrodes have been used with tetraplegics to control robotic arms [92]–[95]. Other studies have also demonstrated paralyzed subjects using Electrocorticography (ECoG) to control a robotic arm [96], and magnetoencephalography (MEG) to control a robotic hand [97]. Scalp EEG has been used with amputees to control the shaping of the hand during the reach of objects [98]. Studies have been performed where able bodied subjects controlled a robotic arms and hands with fMRI [99] with MEG [100], and with scalp EEG [101].

Lower limb prosthetic devices

Powered lower limb prosthetic devices are a relatively recent development in prosthetic technology, with only one commercially available powered ankle[21] and one powered knee.[22] To date, no studies have demonstrated BMI control of a powered lower limb prosthesis. However, myoelectric devices (EMG-driven) have been heavily investigated in the research literature [102]–[105] and are currently under development by a commercial entity.[23] A detailed review of powered lower-limb prosthetic devices and their various specifications, including controls and unique features, can be found here [106].

Powered wheelchairs

BMI-controlled powered wheelchairs provide augmentation and/or restoration of mobility. These devices have been used for research purposes, but currently there is no available BMI-controlled powered wheelchair in the U.S. market. Researchers in this topic have assessed a wide variety of characteristics for signal acquisition, feature extraction, classification algorithm, and control modalities [107]. Moving forward, devices marketed as BMI-powered wheelchairs should establish clearly the method of communication between the brain monitoring technology and the end effectors, the control mechanisms, limitations, and stop systems. Standard performance metrics to evaluate the safety and effectiveness in the use of the device still need to be developed.

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[20] Touch Bionics: "i-digits quantum" 2018; "i-limb revolution," 2018; "i-limb quantum" 2018; "i-limb ultra" 2018. OttoBock: "Michelangelo prosthetic hand," 2017; "Above-elbow prosthesis with DynamicArm," 2017; "AxonHook," 2017; "System Electric Greifer," 2017; "bebionic hand," 2017; "Myoelectric Speed hands," 2017; "Electrohand 2000 for children," 2017. T. Prosthetics, "The Taska," 2018. P. s.r.l.: "IH2 Azzurra," 2018. V. Systems: "Vincent Evolution 2," 2018; "Vincent young," 2018; "Vincent Young 3," 2018; "Vincent Evolution 3," 2018; "Vincentpartial Active," 2018. L. Technology, "Boston Digital Arm," 2018. Utaharm, "Utah Arm 3," 2018.

[21] 1A1-1 Empower, Ottobock.

[22] Power Knee, Ossur. https://www.ossur.com/prosthetic-solutions/products/dynamic-solutions/power-knee (Retrieved on 1 Mar 2018).

[23] Össur Introduces First Mind-Controlled Bionic Prosthetic Lower Limbs for Amputees. Available: https://www.ossur.com/about-ossur/news-from-ossur/1396-ossur-introduces-first-mind-controlled-bionic-prosthetic-lower-limbs-for-amputees (Retrieved on 1 Mar 2018).

Neurostimulation

Peripheral stimulation

Neuromuscular and functional electrical stimulation (FES) systems are commonly available[24] and are used as a tool for diagnosis, as a rehabilitative therapy, or to restore lost function [8]. BMI-FES systems have been used as a tool for rehabilitation where the BMI detects movement intent and FES system stimulates the muscle, essentially actuating the limb. A number of studies have demonstrated BMI-FES systems for rehabilitation of stroke and the spinal cord injury population [8], [108]–[113].

Additionally, effort is being devoted to research on the use of peripheral nerve stimulation as a means to provide tactile feedback to amputees. Recent studies have shown that variation parameters of intra-fascicular multichannel stimulation in median and ulnar nerves allows subjects with transradial amputation to be able to identify tactile characteristics of objects being grabbed by the prosthetics [114]. Similar approaches are also being tested for lower limb prosthetics [115].

Transcranial stimulation

The resurgence, over a decade ago [116], of transcranial brain stimulation has led to a proliferation of research on brain and cognitive augmentation, both in healthy adults and in patients with neurological or psychiatric disease [117]. Augmentation refers to the improvement of cognitive functioning through task performance, or reversal of cognitive deficits that are normal consequences of performance in healthy adults (e.g., fatigue, stress) or those related to brain disorders.

In Transcranial Magnetic Stimulation (TMS) an electric current is transiently passed through a magnetic coil positioned over the participant's scalp over a brain region of interest. This creates a changing magnetic field that passes through the skull and induces current flow in the underlying cortical tissue sufficient to alter neural firing.

Transcranial electrical stimulation (TES) is another technique in which a weak current is applied through scalp electrodes. The most common variant is Transcranial Direct Current Stimulation (tDCS) that uses a weak direct current (DC) electric current (1−2 mA). A positive polarity (anode) is typically used to facilitate neuronal firing whereas a negative polarity (cathode) is used to inhibit neuronal firing. Other variants include the application of oscillatory patterns of electrical current (Transcranial Alternate Current Stimulation, tACS) or random patterns (Transcranial Random Current Stimulation, tRCS).

Intracranial stimulation

The use of invasive neurotechnologies is an important tool to advance our understanding of the brain [33] as well as to treat brain malfunction through intracranial stimulation. The use of deep brain stimulation (DBS) has proven a valuable clinical approach to alleviate symptoms of Parkinson's disease, essential tremor, dystonia, and obsessive-compulsive disorders[118]. In addition, its potential use for other mental illnesses such as depression, obsessive compulsive disorders, or addiction is currently being actively investigated [119], [120]. Currently, these approaches rely on stimulation parameters set by the clinicians that remain fixed (open-loop neurostimulation). More recently, the idea of developing systems that adapt the stimulation parameters (closed-loop neurostimulation) has gained traction as a means to increase the stimulation battery life, and reduce side-effects [121].

Additionally, the use intra cortical micro stimulation (ICMS) approach is being investigated as a technique that can convey tactile-like information to users of neuroprosthetics. In this approach, stimulating electrodes are implanted in the sensory-motor cortex [122], [123]. Typically, in this approach, force measures captured by sensors in the prosthetic limb are translated onto ICMS pulses to evoke different percepts in the user. Experiments on non-human primates have shown that stimuli information (texture, direction of limb movement) can be successfully conveyed in this way.

[24] *Axelgaard* (Available: https://www.axelgaard.com); LGMedSupply; RehaStim; Cyber Medic Stim Plus; Synapse Biomedical Inc. NeuRx DPS; Sigmedics, Inc.; Medel Medicine Electronics; Compex USA; Restorative Therapies; EMS Revolution; Bioness.

Emerging technologies—Optogenetics

Optogenetics combines optics and genetics to control and monitor individual neuron activities in living tissue and precisely measure these effects in real-time. Light is used to control cells in genetically modified living tissue (primarily neurons) to express light-sensitive ion channels. Somatic expression of light-sensitive proteins in the neuronal cell membrane alter the electric state of the neuron upon illumination. However, this technology is still at the stage of animal models. A paper published in 2013 had reported "an injectable class of cellular-scale optoelectronics that offers unmatched operational modes in optogenetics, including completely wireless and programmed complex behavioral control over freely moving animals." [124] Moreover, a paper published in February 2017 reported a flexible subdermal implant incorporating wireless Near-Field Communication (NFC)—for both power delivery and wireless communications—using optoelectronics to target optogenetics applications [125]. A recent study reports a printable transparent μECoG electrode—which demonstrate good biocompatibility suitable for customizable chronic implants—for optogenetic applications by using ultrasonic microfluid printing technique, and could be combined with optogenetics and BMI applications for a possible future use in neurological disease diagnosis and rehabilitations [21].

Augmented /Virtual reality (AR/VR)

VR and AR systems have been developed by numerous commercial entities.[25] BMI-controlled VR and AR systems have been widely explored in the research literature [126], [127], with researchers using varying brain signals and neural features to control objects in virtual environments. Virtual objects vary from anthropomorphic objects, such as human avatars or limbs [128]–[130], to non-anthropomorphic objects and graphical user interfaces [131]–[133]. Among these, the display types vary between a head mounted monitor, computer monitor, transparent video, VR headsets, and AR headsets.

[25]For instance: Oculus Rift; HTC Vive Pro; HTC Vive; Sony PlayStation VR; FOVE; Google VR; Microsoft Hololens; Google Glass; Magic Leap One.

Level of standardization

Existing standards

Table 5—Standards related to end-effector devices

STANDARD	DESCRIPTION
ELECTRICAL	
IEC 60601-1:2005+AMD1:2012, ANSI/AAMI ES60601-1:2005/(R)2012	General safety
IEC 60601-2-10:2012+AMD1:2016	Stimulator safety
IEC 60601-2-40:2016	EMG safety
IEC 60601-1-2:2014, ETSI EN 301 489-1, ETSI EN 301 489-3, BS EN 50561-1:2013	Electromagnetic
IEC 62304:2006+AMD1:2015	Software
IEC 60601-1-10:2007+AMD1:2013	Closed-loop control
ANSI/AAMI HA60601-1-11:2015	Devices for home healthcare
ANSI/IEC 60529-2004	Electrical enclosure
UL 1642 5th Ed.	Lithium Batteries
ISO/WD 7176-14, ISO 7176-4:2008,	Wheelchair power/controls
MECHANICAL	
ISO 10328:2016, ISO 15032:2000, ISO 22675:2016, ISO/TR 22676:2006, ISO/TS 16955:2016, ISO 22523:2006,	Requirements and testing
ISO 7176-6:2001, ISO 7176-2:2017	Wheelchair speed and dynamics
GENERAL	
ISO 14971:2007,	Risk management
ISO 13485:2016, ISO 9001:2015	Quality management of medical devices
ISO 15223-1:2016	Labelling
ISO 10993-1:2009, ISO 10993-10:2010, ISO 10993-5:2009	Biocompatibility
AAMI ANSI HE75:2009/(R)2013	Human factors engineering
AAMI TIR49:2013	Instructional materials
AAMI ANSI IEC 62366-1:2015	Application and usability
ISO 14001:2015	Environmental management
WHO standards for prosthetics and orthotics. Geneva: World Health Organization; 2017. License: CC BY-NC-SA 3.0 IGO.	Global standards for prosthetics and orthotics
DEFINITIONS & TERMINOLOGY	
ISO 8548-1:1989, ISO 8548-2:1993, ISO 8548-3:1993, ISO 8548-4:1998, ISO 8548-5:2003,	Limb deficiencies
ISO 8549-1:1989, ISO 8549-2:1989, ISO 8549-3: 1989, ISO 8549-4:2014	O&P Vocabulary

STANDARD	DESCRIPTION
ISO 8551:2003, ISO 21065:2017, ISO 29781:2008, ISO 29782:2008	Functional deficiencies and rehabilitation
ISO 29783-1:2008, ISO 29783-2:2015, ISO 29783-3:2016	Human gait
ISO 13404:2007, ISO 13405-1:2015, ISO 13405-2:2015, ISO 21064:2017, ISO 21063:2017	O&P components
IEEE Std 1872-2015, IEEE P1872.1, IEEE P7007, IEEE P7008	Robotics
NEUROSTIMULATION	
IEC 60601-2-10	Medical electrical equipment—Part 2-10: Requirements for the basic safety and essential performance of nerve and muscle stimulators
VIRTUAL AND AUGMENTED REALITY	
IEEE P2048.1	Definitions
IEEE P2048.2, P2048.3, P2048.7, P2048.8	Visual
IEEE P2048.9, P2048.10	Audio
IEEE P2014.6	Interface
IEEE Std 3333.1.1-2015	User Experience
IEEE P2048.4	Person Identify
IEEE P2048.5	Safety
IEEE P2048.12	Content ratings
GUIDELINES, GOOD PRACTICES AND OTHER DOCUMENTS	
PROSTHETICS	
K. Bowsher *et al.*, "Brain-computer interface devices for patients with paralysis and amputation: a meeting report," *J Neural Eng*, vol. 13, no. 2, p. 23001, Feb. 2016. [1]	
NEUROSTIMULATION	
J. J. Fins and Z. E. Shapiro, "Deep brain stimulation, brain maps and personalized medicine: Lessons from the human genome project," *Brain Topogr.*, vol. 27, no. 1, pp. 55–62, 2014. [134] B. Nuttin et al., "Consensus on guidelines for stereotactic neurosurgery for psychiatric disorders," J. Neurol. Neurosurg. Psychiatry, vol. 85, no. 9, pp. 1003–1008, Sep. 2014.[119] R. K. Shepherd, J. Villalobos, O. Burns, and D. A. X. Nayagam, "The development of neural stimulators: A review of preclinical safety and efficacy studies," *J. Neural Eng.*, vol. 15, no. 4, 2018. [135] A. J. Woods *et al.*, "A technical guide to tDCS, and related non-invasive brain stimulation tools," *Clin. Neurophysiol.*, vol. 127, no. 2, pp. 1031–1048, Feb. 2016. [136]	
VIRTUAL AND AUGMENTED REALITY	
B. Birckhead et al., "Recommendations for Methodology of Virtual Reality Clinical Trials in Health Care by an International Working Group: Iterative Study," JMIR Ment. Heal., vol. 6, no. 1, p. e11973, Jan. 2019. [137]	

Standardization efforts

For medical terminology related to exoskeletons and prostheses, the International Society for Prosthetics and Orthotics has developed a comprehensive lexicon for Standard Terminology for Prosthetists and Orthotists.

Standards for Wearable Robotics: The ISO is currently developing a standard entitled "*Medical electrical equipment—Part 2-78: Particular requirements for the basic safety and essential performance of medical robots for rehabilitation, assessment, compensation or alleviation*" (IEC/DIS 80601-2-78) under the ISO/TC 299 robotics working group. This standard encompasses numerous end effectors considered within this document, including exoskeletons and prostheses. Additionally, the IEEE Robotics & Automation Society is developing standards for wearable robotics, with the focus being on devices for non-medical applications, such as military, construction, and industrial.

An EU-funded project called EUROBENCH started in January 2018 with the aim of developing a benchmarking framework for robotics. It mainly focuses on bipedal machines (i.e.,exoskeletons, prosthetics, and humanoids). Interestingly, they propose to develop benchmarking facilities for wearable robots and software. Complementarily, another EU-funded initiative: "Inbots Inclusive Robots for a better society" is focused on building a multidisciplinary community that work on aspects of responsible research and innovation paradigms for interactive robotics.

Although it was not meant as a standardization effort per se, the Cybathlon 2016 allowed comparison of the performance of multiple types of robotic end effectors [138], [139]. Prosthetics used by participants included devices that are neither commercially available nor discussed in published literature in addition to some of the devices described above. It should be noticed that in the case of lower limb prostheses, some of these devices are not robotically active from an actuator perspective. A number of devices, including the Genium X3 from Ottobock and the Ossur Rheo Knee, actively monitor the gait cycle to modify the resistance properties of the knee joint; however, they do not actively propel the user through the gait cycle by means of actuation (e.g., electric motor, pneumatically powered artificial muscles).

Synthesis: Priority topics and recommendations

The following terms lack clear definitions within the context of BMI-controlled end effectors and have thus been given a proposed definition:

a) **Active/Passive:** In the context of BMI-controlled robotic end-effectors, active systems are those in which control commands from the BMI system are used to manipulate the end effectors, generally through electromechanical actuation (robotics), digital manipulation of the virtual environment (VR/AR), or onset of electrical stimulation (FES).
b) **Continuous Control:** Continuous control is exhibited by a BMI-controlled system if the user can actively control one or more output of the end effector within an essentially continuous interval through variations in his/her neural activity within a related continuous interval. Continuous control is commonly referred to proportional control within the context of prosthesis and exoskeleton control. The term 'proportional control' is avoided here to prevent confusion with the common control theory also referred to as proportional control (i.e., controller output is proportional to error signal; p-control). Examples of a BMI-controllable output include end effector position, velocity, acceleration, force, electrical current, etc., in either physical or virtual space. Definition adapted from Fougner et al. [140].

c) **State-control:** State control, in contrast to continuous control, describes the ability for the user to control a finite number of discrete end effector states through the modulation of their neural activity. Examples of state control include control of start and stop, control of various hand positions in a prosthesis, left/right wheelchair control, etc. The term digital control is avoided to prevent confusion with modern digital control systems.
d) **Position-zero:** The position of the end effector at its initial resting state. While the exact definition of the starting state is dependent on the specific end effector configuration, it is important that end effector coordinates are provided so that the correct transformation can occur between the BMI output and end effector movement.

Although a comprehensive (but likely not completely exhaustive) list of related standards was provided above, there remain gaps related to current end effector technology.

Established definition and taxonomy of motor functions

End effectors are capable of assuming numerous physical configurations, depending on the design and desired use of the device. In the case of anthropomorphic devices, the end effector attempts to replicate or augment a type of human motor function. Thus, a taxonomy of functions should be developed to provide a standardized language when considering the prescribed use of the device. For example, grasp patterns are a set of unique hand postures that allow the hand to manipulate different objects. A proper definition of grasp patterns is critical when robotic hands are compared in terms of how many grasp patterns they can perform. This can be adapted from medical and anatomy literature, but should carefully consider the definitions in the context of a robotic system.

Omissions of motor functions or degrees-of-freedom

To reduce complexity and costs, anthropomorphic end effectors are often designed to have fewer degrees of freedom than the human body. Examples include replacing a finger joint with a bent solid material, and mechanically coupling the adduction and flexion of fingers. These strategies should be defined explicitly to facilitate control and comparisons in device capabilities.

Standardized data communication to prosthesis

A protocol that would allow systems that extract motor intent (either through neural rhythms in BMI or peripheral activity such as EMG) to command end effectors. A “plug and play” model should allow users to swap similar end effectors and expect the same behavior.

Shared control protocols and human control override

BMIs act to provide discrete or continuous commands to the end effector based on user intent and neural modulations. Within the device, powered end effectors rely on intrinsic feedback to adjust the control parameters (e.g., impedance) and modulate the joint/effector state with relation to some reference (e.g., joint angles during gait). Thus, BMI controlled end effectors employ a shared control paradigm, where user intent guides the end effector, while internal control algorithms act to implement control of the device. In this context, it would be important to consider a risk-assessment based selection of shared control autonomy levels. There is need for standards for shared control architectures that allow for human override during unsafe conditions.

Skin and soft tissue protection

Among the adverse events reported during use of an exoskeleton, skin and soft tissue breakdown is the most frequently occurring injury type [86]. Clinicians refer to a number of management techniques for musculoskeletal injuries [141]–[143], specific guidelines for preventing such injuries during use of an assistive device (e.g., exoskeleton, powered prosthesis) do not exist. Thus, it is imperative that standards

for prevention are developed, as skin issues may prevent the use of a BMI-controlled end effector by otherwise eligible individuals.

Fall prevention and mitigation

Falls pose a significant risk to individuals with impairment, and can lead to further injury, functional impairment, disability, or even death (e.g., in the elderly population [144]). As summarized in He et al. [86], studies often conclude that the risk of falls is low during use of a particular device simply because no falls were observed during experiments. However, the risk of falls simply cannot be ignored and their prevention and management should be standardized for all BMI-controlled end effectors.

Appendix IV—Data representation, storing, and sharing

State of the art in data representation, storing, and management

With the advent of the age of big data and ubiquitous, pervasive computing, human interfacing modalities with systems has evolved from conventional methods to the use of bio-signals. The scope of applications of these systems is not only restricted to clinical domains; they also find widespread applications for the general consumer. With multiple bio-signals being used to control systems (BMIs), there is an emerging need to identify and develop data storage and sharing standards in order to provide the stakeholders the benefits of efficiency and interoperability.

Biosignal datasets, including EEG, EOG, EMG, MEG, fMRI, among others, typically tend to be large datasets that require representation and compression schemes for efficient storage. While previous applications focused on the off-line analysis of such datasets, where processing pipelines were developed to process and learn from recorded datasets, emerging applications in the BMI domain require real-time processing and online learning, bringing additional constraints to the way data is stored and processed. Learning from online data streams is also challenged by the nature of data, as such biosignals are conventionally non-stationary, high-dimensional, and require storage with high precision. Further, the data needs to be annotated with subject-identifying information (suitably anonymized or coded), session and trial information (to represent events of interest that would need to be retrieved/detected subsequently), as well as other relevant metadata. Thus, there is clearly a mandate for identifying efficient data representation and storage mechanisms for various types of bio signals.

The need for data standardization for biosignals is also driven by the requirement for interoperability of data among heterogeneous systems. There are different EEG acquisition systems available and the biosignal recordings generated are often dependent on the hardware being used. As such, system interfaces that require to process these datasets need customized interfacing modules to acquire and/or stream biosignals from the respective acquisition devices. The development of data representation and storage standards is expected to bridge the gap between the diverse data formats prevalent and contribute to greater interoperability across diverse hardware and acquisition devices.

Another vital aspect is data sharing, in the context of healthcare information systems and interfaces. These bio signals are often used and shared between multiple systems, such as Electronic Health Record (EHR) systems, or other data processing nodes of BMI systems. EHR systems are mandated to securely store and transmit bio signals, as identified by existing standards for EHR design and security, such as ISO 18308 and ISO TS 14441 respectively. Bio signals are also shared between processing nodes in BMI systems, and these are also vulnerable to attacks [145], [146]. Thus, secure sharing mechanisms or guidelines also need to be identified. It is important to note that cybersecurity and data management was mentioned by BMI researchers as one of the top priorities for standardization.

Level of standardization

Existing standards

One of the primary data formats for bio signals is the Generic Data Format (GDF).[26] It evolved as a variant of the originally proposed European Data Format (EDF), and overcame several limitations of EDF including the use of a single data type, limited block size, rounding error due to scaling coefficients,

[26] https://en.wikipedia.org/wiki/General_Data_Format_for_Biomedical_Signals

overflow detection, and the inability to store event information. The GDF format is also supported by several acquisition devices and processing toolboxes as well.

There are several other prevalent data formats for BMI data. Examples include easy, info, stim, sdeeg,[27] BCI2000,[28] MFER,[29] XDF.[30] The easy file format represents the data as one line per time sample (across all channels), along with a trigger flag and timestamp. The sdeeg is a proprietary, binary data format that is interoperable with other Neuroelectrics[31] formats. BCI2000 is an elementary data format comprising of a header definition with system parameters and states, and the raw signal data. Medical waveform Format Encoding Rules (MFER) is another standard for biosignals, which enables simple encoding of signals. Extensible Data Format (XDF) supports multiple streams with an XML based header for metadata and data samples representation. It defines generic representation and is extensible to other time series signals as well. Table 6 presents a non-exhaustive list of prevalent standards applicable for bio-signals.

A review of compression techniques applied to multiple bio-signals can be found in the work by Hadjileontiadis et al., 2016 [156]. LabStreamingLayer (LSL) is considered by some as a de facto standard for multimodal recordings. (https://code.google.com/archive/p/labstreaminglayer/).

[27] http://wiki.neuroelectrics.com/index.php/Files_%26_Formats

[28] https://www.bci2000.org/mediawiki/index.php/Technical_Reference:BCI2000_File_Format

[29] http://www.medical-storage.co.jp/MFER/En/Index.htm

[30] https://github.com/sccn/xdf/wiki/Specifications

[31] https://www.neuroelectrics.com/wiki/index.php/Neuroelectrics%27_Wiki

Table 6—Standards related to data representation, storage, and sharing

STANDARD	DESCRIPTION
DATA REPRESENTATION	
ISO 22077-1:2015	Health informatics—Medical waveform format—Published April 2015
ANSI/CTA-2060	Standard for Consumer EEG File Format (Attuned Container Format)
IEEE 11073	Series of personal health device communications standards and projects
IEEE P1752	Draft Standard for Mobile Health Data
IEEE P7002	Draft Standard for Data Privacy Process
ONGOING PROJECTS[32]	
ANSI/CTA-2057	Project on Interoperability Standards Series for Consumer EEG Data—Local Transmission
ANSI/CTA-2058	Project on Interoperability Standards Series for Consumer EEG Data—Event Description
ANSI/CTA-2059	Project on Interoperability Standards Series for Consumer EEG Data—User State Description
ANSI/CTA-2061	Project on Interoperability Standards Series for Consumer EEG Data—Group-level meta-data encapsulation
OTHERS	
	IEEE Industry Connections Activity Big Data Governance and Metadata Management
GUIDELINES, GOOD PRACTICES AND OTHER DOCUMENTS	
Neurodata Without Borders: Neurophysiology (NWB:N). (Link)	
OHBM Council Committee on Best Practices in Data Analysis and Sharing (COBIDAS): - T. E. Nichols et al., "Best practices in data analysis and sharing in neuroimaging using MRI," Nat. Neurosci., vol. 20, no. 3, pp. 299–303, Mar. 2017. [147] - Pernet, C. R., et al. (2018, August 9). Best Practices in Data Analysis and Sharing in Neuroimaging using MEEG. https://doi.org/10.31219/osf.io/a8dhx	
N. Bigdely-Shamlo *et al.*, "Hierarchical Event Descriptors (HED): Semi-Structured Tagging for Real-World Events in Large-Scale EEG," *Front. Neuroinform.*, vol. 10, Oct. 2016. [148]	
A. Blasimme, M. Fadda, M. Schneider, and E. Vayena, "Data sharing for precision medicine: Policy lessons and future directions," *Health Aff.*, vol. 37, no. 5, pp. 702–709, 2018. [149]	
K. J. Gorgolewski et al., "The brain imaging data structure, a format for organizing and describing outputs of neuroimaging experiments," Sci. Data, vol. 3, p. 160044, Jun. 2016. [150]	
C. Holdgraf et al., "BIDS-iEEG: an extension to the brain imaging data structure (BIDS) specification for human intracranial electrophysiology," PsyArXiv, 2018. [151]	
C. R. Pernet et al., "EEG-BIDS, an extension to the brain imaging data structure for electroencephalography," Sci. Data, vol. 6, no. 1, p. 103, Dec. 2019. [152]	
G. Varoquaux et al., "Atlases of cognition with large-scale human brain mapping," PLOS Comput. Biol., vol. 14, no. 11, p. e1006565, Nov. 2018. [153]	
J. T. Vogelstein et al., "A community-developed open-source computational ecosystem for big neuro data," Nat. Methods, vol. 15, no. 11, pp. 846–847, Nov. 2018. [154]	
D. Yatsenko, E. Y. Walker, and A. S. Tolias, "DataJoint: A Simpler Relational Data Model," Jul. 2018. [155]	

[32] Work on projects ANSI/CTA 2057, 2058, 2059, and 2061 is on hold (As of 5th February 2019).

Standardization efforts

Consumer technology association working group (WG3): Interoperability Standards Series for Consumer EEG Data. In particular ANSI/CTA specification 2060, that proposes "a file format for storing several data streams in a single, self-describing, file, with each stream potentially sampled at a different rate, or having a different type (e.g., real numbers and strings). It will allow this data to be provided in an efficient and temporally accurate manner to analysis and visualization applications."[33]

Besides the standardization efforts detailed above, there are also multiple initiatives oriented at providing tools and repositories for sharing neural data. Among these initiatives we can mention the following:

- NeuroData Without Borders—Unified data format for cellular neurophysiology data.
  - Sponsored by: GE, Allen Institute for Brain Science, Howard Hughes Medical Institute (HHMI), Kavli Foundation, and Collaborative Research in Computational Neuroscience (joint NSF & NIH joint program).
  - Scientific Partners: Allen Institute, Svoboda Lab (HHMI), Meister Lab (CalTech), Buzsáki Lab (NYU), and Redwood Center for Theoretical Neuroscience (UC Berkeley).
- Neuroscience Information Framework (NIF)—Open source network providing dynamic, searchable inventory of neuroscience resources, including public research data, learning materials, and tools (all publicly accessible via the Internet).
  - NIF is an initiative of the NIH Blueprint for Neuroscience Research
- Brain-CODE—Networked database established by Ontario Brain Institute for sharing brain research data between >40 research sites across Ontario, Canada.
  - Clinical areas of research focus include cerebral palsy, depression, epilepsy, neurodegenerative disorders, and neurodevelopmental disorders.
- NeuroData—"Building and deploying open source data-driven tools that run at scale on open access data. This includes analytics, databases, cloud computing, and Web-services applied to both big neuroimages and big neurographs."
  - Project focuses on mapping the anatomic and functional connectivity of the brain, including "Synaptomes", "Connectomes/Projectomes."
- Project Data Archive for the Brain Initiative (DABI)—This NIH-funded project focuses on the development of "*web-accessible data archives to capture, store, and curate data related to the BRAIN Initiative proposals that collect invasive human neurophysiological data and make them broadly available and accessible to the research community.*"
- Brain Imaging Data Structure (BIDS) [150]—A community-driven standard inspired by the format used in the OpenNeuro.org repository (formerly OpenfMRI) to organize and share data from (fMRI-based) neuroimaging experiments. This standard has been recently extended to cover experiments with intracranial EEG (BIDS-iEEG) [151].
- IEEE DataPort—A data platform provided by IEEE that enables users to store, search, access, and manage datasets. This platform is intended to facilitate analysis of datasets and retains referenceable data for reproducible research.

The International Neuroinformatics Coordinating Facility (INCF)[34] is a non-profit organization with the stated mission of advancing the field of neuroinformatics. One of its proposed goals is to provide a library

[33] https://standards.cta.tech/kwspub/current_projects/

[34] https://www.incf.org/about/who-we-are

of endorsed community standards and best practices according to the FAIR principle.[35] As of December 2019, they have endorsed Brain Imaging Data Structure (BIDS) (see link above), as well as NeuroML and PyNN, a language and simulator for cell, channel, and synapse models.[36]

Synthesis: Priority topics and recommendations

As listed above, multiple ongoing efforts are devoted to build brain atlases that combine imaging recordings at different scales. These efforts have independently created impressive infrastructure for the curation, annotation, cleaning, and visualization of data. However, they may lead to disjointed resources that may not be able to interoperate among them.

In addition, relevant to BMI technologies, all these efforts are focused on the storage and offline use of neural data and are not necessarily suited to fulfil the inherent needs of real-time closed-loop interaction. Thus, it is important to devise how this infrastructure could be extended to accommodate these needs.

Standardization gaps also exist on issues related to cybersecurity, which include **data reliability, protection, and encryption**. This has been proposed as one of the priority areas in upcoming years. In a time where more industrial actors are entering into the development of BMI systems (e.g., Facebook currently works on systems for decoding silent speech) it is important to come up with solid ways for ensuring encryption and to set filters on the type of information that can be read and accessed. One of the current drawbacks is that there is no legal agreement on what personal information is, nor on how this information can be shared or processed. This issue also extends to information that is in danger of being extracted by devices (the same is true for other health-related devices like wearable activity monitors). This topic implies not only to the information a device provider may extract from the users, but also unauthorized third party access (i.e., standard on cyber-security on the devices).

An unexpected use of this information may be intentional manipulation, as it happens with information through social media. The same way that social media can be used to create buzz and manipulate. Processed brain data and its interpretation could be manipulated to steer users towards specific directions. Particularly in the cases of consumer applications, it would be important to assess the reliability of the collected data (e.g., identify what the real data origin is: e.g., brain, muscular, or even fabricated activity), as well as its interpretation. For example, applications like lie detectors or gaming are not regulated. In these cases, the standards focus on performance metrics (according to their claims) of safety, but not their efficiency. A similar situation is observed on wearable activity monitors; e.g., Fitbits have similar levels of accuracy among them, but not standardized with other brands.

In this respect, it is worth noticing that in December 2016 the FDA released their guidelines on cybersecurity.[37] They state that "*Digital connections power great innovation—and medical device cybersecurity must keep pace with that innovation. The same innovations and features that improve health care can increase cybersecurity risks. This is why we need all stakeholders in the medical device ecosystem to collaborate to simultaneously address innovation and cybersecurity. We've made great strides but we know that cybersecurity threats are capable of evolving at the same pace as innovation, and therefore, more work must be done*."

[35] FAIR: Findable, Accessible, Interoperable, and Reusable principles for data sharing.

[36] https://www.incf.org/resources/incf-endorsed-standards-best-practices.

[37] https://blogs.fda.gov/fdavoice/index.php/2016/12/managing-medical-device-cybersecurity-in-the-postmarket-at-the-crossroads-of-cyber-safety-and-advancing-technology/.
http://www.raps.org/Regulatory-Focus/News/2017/01/03/26496/FDA-Finalizes-Postmarket-Cybersecurity-Guidance/.

Guidelines require manufacturers to:

- Have a way to monitor and detect cybersecurity vulnerabilities in their devices
- Understand, assess, and detect the level of risk a vulnerability poses to patient safety
- Establish a process for working with cybersecurity researchers and other stakeholders to receive information about potential vulnerabilities (known as a "coordinated vulnerability disclosure policy")
- Deploy mitigations (e.g., software patches) to address cybersecurity issues early, before they can be exploited and cause harm

The FDA guidance also recognizes the ISO standards, *ISO/IEC 30111:2013: Information Technology Techniques – Vulnerability Handling Processes* and *ISO/IEC 29147:2014: Information Technology – Security Techniques – Vulnerability Disclosure*.

Appendix V—User Needs

State of the art in addressing BMI user needs

The clear and comprehensive definition of user needs is an essential foundation for the development of any commercial technology, as they form the basis upon which user satisfaction and product effectiveness are ultimately evaluated. The primacy of user needs in product design is especially true of medical devices, for which the processes of design verification and validation are defined relative to documented design requirements and the user needs from which they originate, respectively. This relationship between user needs, design requirements (input), and the resulting device design (output) can be easily visualized using a traditional Waterfall Design Process diagram, as depicted in the FDA Guidance on Design Controls for Medical Device Manufacturer's [157] (Figure 9). Viewed in this way, user needs may be understood as a primary source of design input (along with regulatory requirements and additional business requirements), and the fulfillment of user needs as the ultimate measure of successful design.

However, given the necessary applicability of design controls to a wide variety of devices, neither the FDA Guidance Document on Design Controls nor the Quality System Regulations to which it applies (FDA 21 CFR 820.30 and ISO 9001, Subclause 4.4) prescribe precise practices to be used in the implementation of design controls, including the definition and validation of user needs. Rather, the collective body of medical device regulations and regulatory guidance on design controls merely impose a general framework that affords device manufacturers considerable flexibility to craft design controls suitable for their respective product design and development processes.

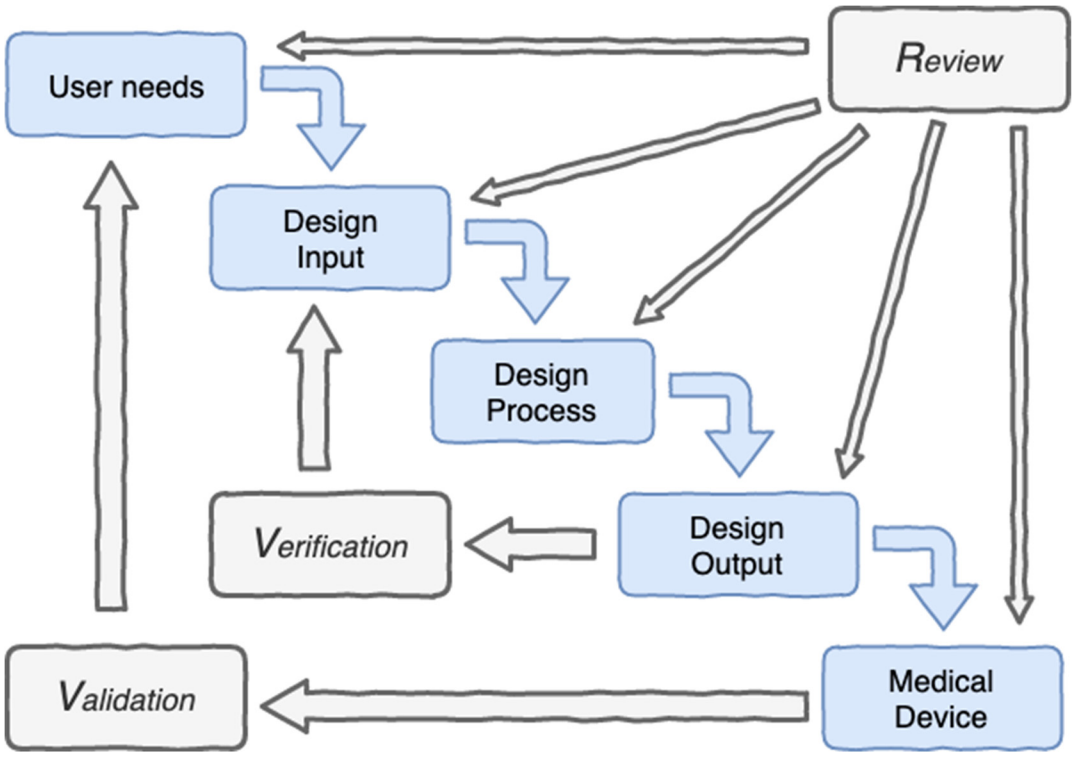

Figure 9—Design controls for medical devices, depicted as Waterfall Design Process

Adapted from the FDA Design Control Guidance for Medical Device Manufacturers (docket ID no. FDA-2013-S-0610)

Consequently, the identification and process for defining user needs remains poorly standardized, and typically left to the discretion of device developers. In practice, the definition of user needs is commonly performed *post-hoc* by developers already well along in the design process, with limited input from representative prospective device users. The potential for such distortion of the proper design process is greater still in BMI technologies used for non-clinical applications such as video gaming or personal relaxation, and thus beyond the scope of medical device regulation.

While this regulatory leeway is often favorable to device manufacturers in the short term, further standardization of user needs and the process for defining them is warranted to facilitate the development of a more interoperable ecosystem of neurotechnology for BMIs. Because BMI technologies span such a wide range of modalities, applications, and users, it is essential for this standardization framework to remain sufficiently broad and adaptive to accommodate this technological and user diversity, yet adequately specific to ensure desired levels of interoperability. Ultimately, the development of such a 'plug & play' ecosystem will benefit device developers and end users alike, in addition to auxiliary benefits of reduced device cost and regulatory complexity. Accordingly, the present document aims to summarize the existing standards, guidance documents, and *de facto* paradigms in the area of BMI user needs, as a foundation for recommendations for further standardization.

Segmentation of BMI User Population

As true for any user-(inter)facing technology, a lucid and useful discussion of BMI user needs must be rooted in an accurate characterization of the complete Neurotech user population. Indeed, the BMI user population is unique in its breadth and diversity, and the development of prescriptive recommendations and standards demands delineation between user types.

At the highest level, Shah and colleagues [169] posit that two broad classes of users be considered in the development of any medical device: end users (typically patients and/or lay caregivers), and (healthcare) professional users, including physicians, nurses, and clinical technicians. In the case of the most current BMI technologies, developers must further account for the needs of professional *researcher* users, who are often the *primary* technology users, and whose needs are sufficiently distinct from both lay end users and healthcare professionals to warrant consideration as a separate class of user. Naturally, each of these user classes may be further sub-categorized, as depicted in Figure 10.

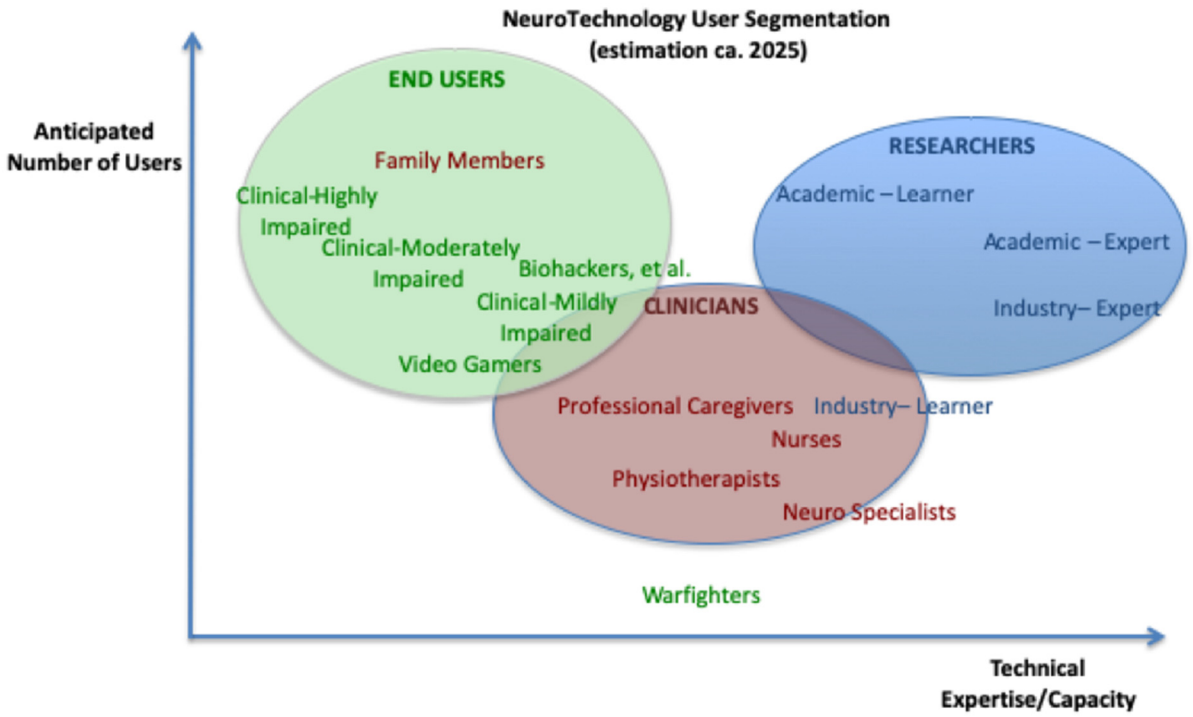

Figure 10—Classification and segmentation of BMI user types

Though overlap in user needs between the previous classes is inevitable, such overlap should not be assumed, nor should users from one class be taken as representative of those from another. Rather, user needs should be identified through dedicated and separate process for each of the three major classes (as applicable). Depending on the particular application and corresponding user base, such independent definition of user needs may be necessary between various sub-classes as well.

Level of standardization

Existing standards

The primary standards pertaining to the definition and evaluation of BMI/neurotechnology user needs are outlined in the main body of this document (User Needs section), summarized in Table 7, and further detailed in Table 8. To summarize at a high level, recognized standards and best practices addressing BMI user needs are scattered across three major classes of document: official consensus standards, published regulatory guidance documents, and clinical/scientific literature. Within each class, documents vary in their scope, with some identifying specific user-related requirements, and others describing *processes* for defining and testing user needs. Likewise, published standards and recommendations may differ in their applicability to different BMI modalities and user populations.

Synthesis: Priority topics and recommendations

Areas with good standardization:

- General Human factors/Usability Engineering processes
- Medical Device Design Controls: provides general framework for incorporation of user needs in design process for medical device

- Specific user needs for severely disabled (highly dependent) clinical end users: spinal cord injury, locked-in syndrome, etc.

Areas needing further development/standardization:

- Identification and evaluation of user needs for needs for wider range of BMI users and use cases, including healthy users and mildly-to-moderately impaired clinical users
- Development and differentiation of user needs for different *classes,* including physicians and lay caregivers
- Standard instruments and methods for evaluating usability and fulfillment of user needs (benchmarking)
- Development of standardization of user needs and *rights* related to neurodata security, privacy, ownership, and neuroethics
- Customization of general usability-related standards and templates for particular well-developed BMI technologies and user types
- Guidelines for user education, training, and instructions for use of BMI/NeuroTech systems, with emphasis on improving usability
- Standard terminology for usability-related cognitive states and tasks

Table 7—Standards related to user needs

STANDARD	DESCRIPTION
STANDARDS AND REGULATIONS	
IEC/ISO/AAMI 62366:2015 [Cor-2016]	Usability Engineering for Medical Devices
ISO 14971:2019	Application of risk management to medical devices
IEC 60601-1-6 :2010 + AMD1:2013 CSV	Medical electrical equipment -- Part 1-6: General requirements for basic safety and essential performance -- Collateral Standard: Usability
21 CFR 820.30 [2018]	U.S. Code of Federal Regulations – Design Controls (for medical devices)
ISO 9241-11	Ergonomics of human-system interaction – Usability: Definitions and Concepts
ISO 9241-210	Ergonomics of human-system interaction -- Human-centered design processes for interactive systems
GUIDANCE, RECOMMENDATIONS, AND BEST PRACTICES	
ANSI/AAMI HE75:2009/ (R)2018	Human Factors Engineering—Design of Medical Devices
FDA Guidance (docket No. FDA-2011-D-0469) [2016]	Applying Human Factors & Usability Engineering to Medical Devices
FDA Guidance (document No. document number 1500045) [2019 - Draft]	Implanted Brain-Computer Interface (BCI) Devices for Patients with Paralysis or Amputation—Non-clinical Testing and Clinical Considerations
FDA Guidance, docket ID: FDA-2013-S-0610	Design Control Guidance for Medical Device Manufacturers
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Table 8—Standards, regulations, and regulatory guidance concerning user needs

Document ID [Year]	Title	Type	Specificity Level	Scope (Summary)	Key Points
IEC/ISO/AAMI 62366:2015 [Cor-2016]	Usability Engineering for Medical Devices	International Consensus Standard	All Medical Devices	• Specifies a *Process* for a *Manufacturer [MFG]* to analyze, specify, develop, and evaluate the *Usability* of a *Medical Device* as relates to *Safety* (Part 1). • Allows the MFG to assess and mitigate *Risks* associated with *Correct Use* & *Use Errors* • Part 2 provides more detailed descriptions of UE methods that can be applied beyond safety aspects of med device UIs	• Defines *Usability* in accordance with ISO 9241, with respect to device *Effectiveness*, *Efficiency*, and *User Satisfaction* in the intended *Use Environment* ○ Distinguishes *general effectiveness* (defined as the accuracy and completeness in accomplishing a given goal) from *clinical effectiveness*, as assessed in the clinical trial of a medical device. • Equates usability and human factors engineering (UE/HFE) • UE/HFE clearly identified as part of the Risk Management process for medical devices, with strong reference to ISO 14971 • UE process begins with Use Specification document -- including intended indication(s)/environment for use, user profile(s), user interaction with device, and device operating principle(s) -- followed by identification of the user interface (UI) characteristics related to Safety, potential Use Errors, and hazards **Gap:** Incumbent on device makers to establish and maintain their own specific process for defining the user needs and resulting req'ts
ISO 14971:2019	Application of risk management to medical devices	International Consensus Standard	All medical devices	• Defines risk mgmt process for med devices, including med device software • Designed to identify device-related hazards and evaluate associated risks, control the risks, and monitor the effectiveness of controls • Does not apply to business risk or to clinical decisions regarding when to use a given device	• Requires med device Mfgs to establish objective criteria for *Risk* acceptability, but does not specify acceptable *Risk* levels • Defines *Risk* as the combination of the probability of occurrence of harm and the severity of the potential harm – because use-related hazards, usability is implicated • Fundamental integration of risk mgmt with design controls: Hazards and Hazardous Situations are expected to feed into Design Ctrls via definition user needs & design inputs • End users must be included in the Risk Mgmt Process **Gaps** • Non-specific to BMI/neurotech. • Addresses user needs only insofar as applicable to mitigating user and usability-related risks → resulting focus on safety, without direct regard to user goals or device usability (effectiveness, efficiency, user satisfaction)
IEC 60601-1-6 + AMD1:2013	Medical electrical equipment—Part 1-6: General requirements for basic safety and essential	International Consensus Standard	Medical Electrical Equipment	• "Specifies a [*Usability Engineering (UE)*] *Process* … to analyze, specify, design, *Verify* and *Validate Usability*, as it relates to *Basic Safety*	• UE Process that references and complies with IEC 62366 and ISO 14971 • Device manufacturer (Mfg) required to establish UE Process • Mfg req'd to establish acceptance criteria for Usability

Document ID [Year]	Title	Type	Specificity Level	Scope (Summary)	Key Points
	performance—Collateral Standard: Usability			and *Essential Performance* of *Medical Electrical Equipment*" • Assesses & mitigates *Risks* caused by *Usability* problems associated w *Normal Use* (*Correct Use* + *Use Errors*)	• Mfg must demonstrate the Usability acceptance criteria are satisfied **Gaps** • Non-specific to BMIs or neurotech • Focused at process level, thus leaving it incumbent on Mfgs to establish their own processes and acceptance criteria • Can be used to identify but does not assess or mitigate *Risks* associated with *Abnormal Use*.
ISO 9241-11	Ergonomics of human-system interaction – Usability: Definitions and Concepts	Int'l Consensus Standard	All interactive systems, products, and services	Defines "usability" and provides framework for applying it to interactive systems (including built environments), products (including industrial and consumer products), and services (including technical and personal services).	• Usability DEF: "extent to which a system, product or service can be used by specified users to achieve specified goals w effectiveness, efficiency , and satisfaction in a specified context of use." • Applicability of "usability" expanded to apply to all aspects of use, including learnability, regular use, accessibility (to users of different capabilities), maintainability. • Concept of usability includes user-specific personal needs, including potentially conflicting sub-goals (e.g., speed versus accuracy). • Concept of effectiveness includes (lack of) negative consequences. • Assessment of effectiveness requires both objective and subjective measures of success. • Satisfaction redefined to account for a wider range of concerns that are now recognized as important for user experience.
ISO 9241-210	Ergonomics of human-system interaction -- Human-centered design processes for interactive systems	Int'l Consensus Standard	All systems with computer-based user interfaces	Req'ts, recs, and principles for HCD throughout the life cycle of computer-based interactive systems. Concerned with both hardware and software aspects/influences on human–system interaction.	• Human-Centered Design (HCD) defined as "approach to systems design and development that aims to make interactive systems more usable by focusing on the use of the system and applying human factors/ergonomics and usability knowledge and techniques."
21 CFR §820.30 [2018 – last rev]	Code of Federal Regulations, Title 21 – Food & Drugs; Part 820 – Quality System Regulation; Section 820.30 – Design Controls	Regulation (U.S.)	All Medical Devices	Generic design control process for medical devices, starting with user needs as foundation	• The design control process for med devices is a rigorous and iterative process (incl. design verification & validation) whereby the design of a product is confirmed to fulfill the user needs. • Design requirements must address the needs of the user/patient, as appropriate based on the intended use of the device. **Gaps:**

Document ID [Year]	Title	Type	Specificity Level	Scope (Summary)	Key Points
					• Definition of specifications to ensure compatibility between system modules is left to the device developers
ANSI/AAMI HE75:2009/ (R)2018	Human Factors Engineering - Design of Medical Devices	Rec'd Practice	All Medical Devices	General human factors engineering (HFE) principles, specific HFE principles geared towards certain user-interface attributes, and special applications of HFE (e.g., connectors, controls, visual displays, automation, software–user interfaces, hand tools, workstations, mobile medical devices, home health care devices).	• Emphasizes user-centered focus throughout the product design & development process, with the goal of making med devices easier to use and less prone to use error. • General Principles of HFE Include: ○ include user input early & often in design process ○ Consider context of use ○ Consider accessibility by a diverse range of users ○ Don't rely heavily on training or expect users to become masters (error tolerance) ○ Be selective with functions left to users versus automated by system ○ Limit user workload (cognitive + physical) ○ Anticipate worst scenarios, incl. both user error & device failures
FDA Guidance (docket No. FDA-2011-D-0469) [2016]	Applying Human Factors & Usability Engineering to Medical Devices	Regulatory Guidance	All Medical Devices	General application of Human Factors and Usability engineering to medical Devices, with primary focus on ensuring device safety and efficacy	• FDA Considers of HFE part of the risk management process • Safety and efficacy are to be considered *specifically for intended users, uses, and use environments* • Rec that HFE/UE process begin with definition of users, use environments, and UI, and base user req'ts on these definitions • "…manufacturer should conduct appropriate HF studies, analyses, and tests from the early stage of the design process…" • "user error is… considered a nonconformity because HF… should [be] considered during the design phase" **Gap:** Definition of specifications to ensure compatibility between system modules is left to the device developers
FDA Guidance (document No. document number 1500045) [2019 - Draft]	Implanted Brain-Computer Interface (BCI) Devices for Patients with Paralysis or Amputation - Non-clinical Testing and Clinical Considerations	Regulatory Guidance (Draft)	Implanted BMI systems	General study design rec's for investigational device exemption (IDE) feasibility and pivotal clinical studies, as well as non-clinical testing, of implanted BCI devices that interface with the nervous system to restore motor and/or sensory capabilities in patients with paralysis or amputation.	• Encourages and recognizes the need for modularity • acknowledges variability in needs (and risk tolerance) among individual patients (users) • Risks & benefits should be assessed relative to intended users **Gaps:** - No formal definition of user needs/requirements - No process for defining user needs/requirements - No specific user needs identified - Std defines UE process with respect to safety, not usability - Does not assess or mitigate risks associated with abnormal use. (…but may be used to identify such risks)

Appendix VI—Performance assessment and benchmarking

State of the art in BMI performance assessment and benchmarking

The assessment of BMIs typically covers both the hardware and software assessments. The hardware includes acquisition devices, form factors, and electronics, and is a key component of BMI performance. Software primarily relates to interface (and stimulation types) and machine learning techniques. Nonetheless, there is not a formal way to effectively assess the impact of performance of these individual elements to the overall performance of the BMI system [174].

Data acquisition benchmarks

Data acquisition hardware is an essential component of BMI performance, whose evaluation is poorly covered. Specifically, one typically relies on a set of hardware specifications provided by the manufacturer. Topics covered in the section devoted to sensors (Appendix II) are hence relevant to this issue.

Physiological metrics

As mentioned before, though informative, the above metrics cannot always be directly related to BMI performance. For instance, the lower cut-off frequency is only relevant to some BMI applications actually making use of lower frequencies. In addition to that, these specifications always need to be placed in the perspective of a real acquisition: the input impedance of an amplifier is mostly informative with a typical range of inter-electrode impedances for a given set of headset/electrode. Hence the importance of assessing the acquisition devices in their context of use (i.e., with a real acquisition).

In general, though one ultimately wants to quantify the ability of a system to measure meaningful neurophysiological changes. Those can vary for each setup, electrode localization, and subject inter and intra-variability leading to a great number of sources of variability that need to be taken into account while benchmarking hardware solutions. A way to control these variabilities is to identify a set of controlled acquisitions in enough subjects to characterize inter-individual variability. For instance, we can look at specific EEG conditions and try to circumvent undesired sources of variability (subject/electrode) to concentrate on the one we want to assess (electronics, electrode, etc.). Similar metrics can be derived for other acquisition techniques.

Table 9—Example of possible benchmarks for EEG acquisition

Recording condition	Metrics	Comments
Resting state EEG	Spectrum; Complexity and information theory metrics	Compare those to expected values in clean EEG. Conceptually very close to a universal univariate signal quality index (SQI).
Resting state EEG	Proportion of epochs with clean SQI (e.g., [175])	Similar metrics will assess the stability of signal over time; obviously, this metric will factor in movement artefacts and will be extremely sensitive to recording conditions and favor wet systems over dry electrodes (more sensitive to movements).
Eyes Closed	EO/EC SNR	A clear and stable neurophysiological marker that can be used to capture oscillatory patterns. Sensitive to user and electrode placement.
Event Related Potential	ERP SNR	Exogeneous ERPs tend to be more stable across individuals than later potentials but they are also more sensitive to input stimulation (type, amplitude, frequency, ...) making comparison difficult. Cognitive ERPs like IEEE P300 are more central (Pz-Cz) so more frequently available but also more variables from one individual to another. The averaged ERP energy over either: ▪ baseline activity whenever available ▪ or the ERP variability as a proxy for noise (c.f., [176], [177] on how to use this marker for comparison purposes)

Software Benchmark

Software is by far the component of BMI that has dragged the most resources leading to very broad literature comparing methods and paradigms. The evaluation metric is hopelessly dependent on the application. To simplify the problem, one can already distinguish well establish processing steps of a BMI and suggest standard evaluation procedures for the following:

- **Pre-processing techniques**: transform a waveform to another waveform with same dimensionality in an attempt to increase SNR: in this case, the Physiological Metrics listed above can be relevant to assess the performance of the pre-processing.
- **Signal Quality Indices:** a method taking a waveform as an input and providing a univariate (or multivariate time series of same dimension) binary output indicating either the signal is considered as clean or noisy; likewise, the physiological metrics listed above can be derived with and without the use of a SQI to assess its performance.

Once a reliably denoised and clean signal is available, it is then transformed to map a feature of the brain's activity for one of the following applications:

- Control of mechanical object in space: wheelchair, robotic arm, drone, cursor on screen, etc.
- Control of a communication device: IEEE P300 speller, mCode applications, and continuous applications
- Monitoring of a mental states: mental workload, fatigue, working memory, etc.
- Operant conditioning on a population of neural network (neurofeedback)

For each of these applications, it will be important to separate the evaluation of the mapping methods (machine learning algorithm) to that of the interface that certainly has an influence on the performance as far as closed-loop BMI are concerned (BCI and neurofeedback devices). A recent article that reviews BCI software: *P Brunner and G Schalk, Brain–Computer Interfaces Handbook: Technological and Theoretical Advances, Chapter 17 BCI Software, 2018.*

Evaluation of machine learning methods

BMI performance is usually assessed using metrics borrowed from the pattern recognition field (e.g., classification, accuracy, sensitivity, specificity). These metrics only reflect part of the BMI functionality and neglect aspects related to the user perception, cognitive workload, or acceptability of the systems. Moreover, they often assume static evaluation conditions and do not take into account the characteristics of the intended application or the contribution end-users may have.

Machine learning metrics of performance

Loss functions estimating the performance of a given machine learning algorithms are a field on its own and are certainly beyond the scope of this document. For reference, we present in Figure 11 a list of the main metrics usually used to assess method performance.

It has to be noted that, in the case of multi-class applications, not all of these metrics are relevant and are Global (e.g., Log likelihood, Precision, Recall/Sensitivity, F1-score, Accuracy, Confusion matrix) or class-dependent (Precision, Recall/Sensitivity, F1-score).

		Predicted condition			
	Total population	Predicted condition positive	Predicted condition negative		
True condition	Condition positive	**True positive**	**False negative (Type II error)**	True positive rate (TPR), **Recall, Sensitivity,** probability of detection = Σ True positive / Σ Condition positive	False negative rate (FNR), Miss rate = Σ False negative / Σ Condition positive
	Condition negative	**False positive (Type I error)**	**True negative**	False positive rate (FPR), Fall-out, probability of false alarm = Σ False positive/Σ Condition negative	True negative rate (TNR), **Specificity** (SPC) = Σ True negative / Σ Condition negative
	Prevalence = Σ Condition positive / Σ Total population	Positive predictive value (PPV), **Precision** = Σ True positive / Σ Predicted condition positive	False omission rate (FOR) = Σ False negative / Σ Predicted condition negative	Positive likelihood ratio (LR+) = TPR/FPR	Negative likelihood ratio (LR−) = FNR/TNR
Accuracy (ACC) = (Σ True positive + Σ True negative) / Σ Total population		False discovery rate (FDR) = Σ False positive / Σ Predicted condition positive	Negative predictive value (NPV) = Σ True negative / Σ Predicted condition negative	Diagnostic odds ratio (DOR) = LR+/LR−	
				F1 score = 2 / (1/recall+1/precision)	

Figure 11—Extended confusion matrix for evaluation performance of discrete classification (transposed from Wikipedia)

All metrics reported in Figure 12 optimize the number of true positives (TP). Sensitivity corrects for Type II error (False negatives). Precision corrects for Type-I error. F1-Score combines both. An alternative approach is to use the mean column-wise AUC as used for instance in the Kaggle competition on Grasp and Lift EEG detection.

In contrast, other applications like the control of a robotic arm require a continuous outcome to be estimated from the brain activity. Commonly used loss functions are the root mean square error: sensitive to outliers but relates to physical units; the correlation with the intended output or Cross-Entropy. However, these metrics have also their limitations [178].

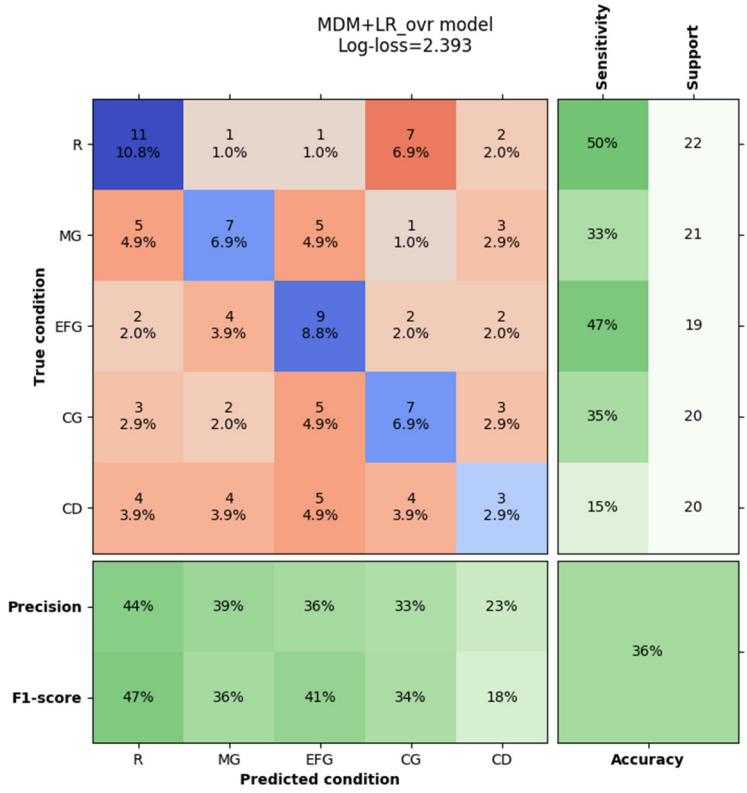

Figure Note—Lines indicates true labels and columns predicted labels so that the diagonal is the multiclass accuracy (summarized in the bottom right corner).

Figure 12—Illustration of a suggested confusion matrix (partly inspired from [179]) showing relevant information for the classification of different motor imaginary movements

Meaningful metrics of performance

Loss functions are typically implemented to the purpose of algorithm optimization and focus mainly on the decoding aspects of the BMI loop [174]. However, they may not always be the best tools to assess the performance of a system for a user. One proposed alternative is to assess the "real accuracy" (i.e., the actual number of correct characters rather than the algorithms' accuracy) as a metric to compare performance and place the accuracy in perspective with bit rate, which ultimately relates to the reliability and speed, respectively, both indispensable to create a useable interface [180]. Also, as illustrated in Figure 13 to be truly meaningful to the application, all results reported should be adequately cross-validated.

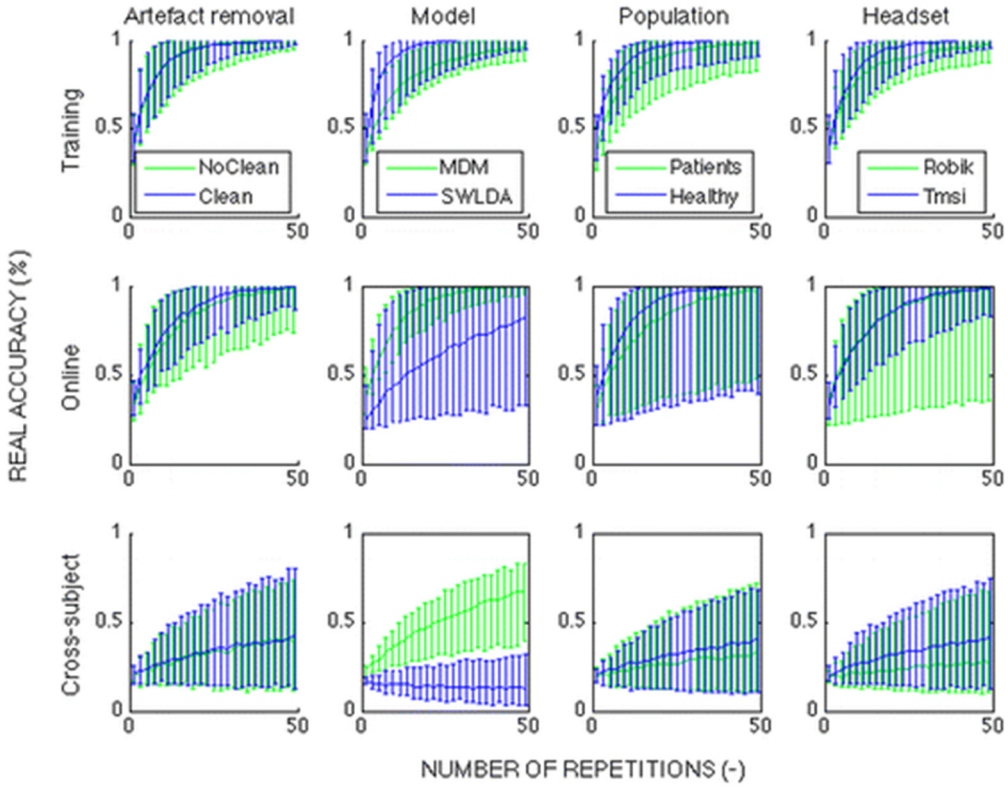

Figure 13—Bit-rates (bits per minutes) evolution for increased number of repetition of IEEE P300 paradigm computed for different pre-processing technique, model, population, and headset using three cross-validation schemes: training, online, and cross-subject

Likewise, for when considering a BMI application based on SMR detection one might like to report on different loss-function depending on the exact application. For instance, a neurofeedback application should reduce the Type I error, i.e., the false positive rate because this is what would impact learning the most. However, false positive rate is ill-defined in a multi-class problem, which is why precision is preferred. Alternatively, a SMR-based BMI application designed for control and not learning) might be more tolerant to Type I error (undesired movement) using dedicated control algorithms at a higher level in the application (smoothing of command in the robotic arm) but less so on Type II error (subject would like to move but cannot) which can be perceived as more frustrating by this population of users (c.f. [181]). Several metrics have thus been proposed to evaluate performance of BMI systems (c.f., [182]–[184]) but there is no consensus on which metrics should be applied.

Level of standardization

Existing standards

Performance assessment and benchmarking of BMI systems is seen as one of the top priorities for standardization. Despite large efforts devoted to evaluating these systems, no specific standard has been developed. Currently, evaluation of these systems is done by individual groups without homogeneous approaches. Table 10 summarizes some current efforts on this domain.

Standardization efforts

As noted before, although some efforts have been made on quantifying the performance of independent components of the BMI loop, there are no comprehensive standards or benchmarks for BMI systems as a whole. Specific studies have been done to evaluate these systems in closed-loop and

use these evaluations for optimizing the system parameters. For instance, Sellers et al. 2006 have also used bitrate to optimize the matrix size and inter-stimulus interval [185]. More recently, Ryan et al. 2017 use the accuracy of a speller application to choose the best color stimulation [186].

Recently, there have been some efforts to develop benchmarks for BMI systems. These efforts mainly consisted of standardized databases made public to allow developers to test their methods, and are usually framed in terms of competitions or challenges (c.f., [187]–[189], or Kaggle). Correspondingly, new initiatives are aimed at providing methods to evaluate the quality of the EEG signal[38] [190], [191] or for benchmarking multiple BMI algorithms [192].

An interesting case is the BCI race competition that took place in part of the Cybathlon 2016 [138], [139]. In this case, multiple teams used a SMR-based BMI to control an avatar in a video game and teams competed to complete an obstacle race in the shortest time. This provided a benchmark task for this type of system where performance was intrinsically linked to the overall achievement of the task, instead of assessing individual elements in the loop. Interestingly, analysis of the system that achieved the shortest time indicates that the training process with the user, as opposed to optimization of the machine learning algorithms, played a key role to achieve high-performance [193].

Synthesis: Priority topics and recommendations

There is currently no consensus on the way the performance of BMI systems should be evaluated. Although there is a plethora of metrics to assess the decoding elements of a BMI, the actual impact of this aspect in the closed-loop performance is far from being trivial. This is even more relevant when the BMI applications allow some level of autonomy in the device to be controlled (e.g., by means of shared control). It is therefore a priority to promote efforts to identify and adopt performance metrics to be applied by the community as a whole. Development of a standardized evaluation method will be crucial to allow comparison of multiple heterogeneous systems.

[38] https://github.com/alexandrebarachant/eeg-amplifier-benchmark.

Table 10—Standards related to performance assessment and benchmarking

STANDARD	DESCRIPTION
ISO 14155	Clinical Investigation of Medical Devices for Human Subjects - Good clinical practice
ISO 10993	Biological Evaluation of Medical Devices
ISO 23640	In Vitro Diagnostic Medical Devices—Evaluation of stability of in vitro diagnostic reagents
STANDARDS IN DEVELOPMENT	
IEEE P2794	Draft Standard for reporting in Vivo Neural Interface Research
IEEE P2731	Draft on Standard for a Unified Terminology for Brain-Computer Interfaces
GUIDELINES, GOOD PRACTICES, AND OTHER REFERENCES	
SFN Research Practices for Scientific Rigor: A Resource for Discussion, Training, and Practice. (Link)	
FDA Guidance for Industry – Q9 Quality risk management. https://www.fda.gov/media/71543/download	
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Appendix VII—Testimonials

Michael Smith, PhD – U. California Berkeley, USA. Statement on standards for consumer-oriented neurotechnologies

"We expect that, as technology develops further in the future, the accuracy of wearable, non-invasive consumer-grade devices for brain activity measurement and recognition will eventually meet or exceed the performance of current medical devices.

Therefore, standards for such consumer-grade devices should be developed so that in the future, as their accuracy increases and new capabilities arise, they also encompass standards for clinical medical devices

[The vision], is that, by using standards, we can encourage the development of low cost neurotechnologies to better help humanity. For example, we believe that a lot of money will be put into the development of low-cost wearables, e.g., EEG headsets, for gaming and other consumer uses. In gaming, the ability to deliver reliable, high-resolution measurements that can deliver an extra degree of freedom will be of enormous value, with the expectation that market-competition will drive these devices to eventually exceed the performance of clinical devices. By writing the standards for consumer-grade devices carefully so that they also "encompass standards for clinical medical devices," e.g., interoperability, etc., as they evolve in accuracy, this enables the development of low-cost devices which can also be used for clinical purposes, making low-neurotechnologies available for all. Of course, there is no guarantee that this will happen, but the payoff is big if it does, so everyone feels it is worth a try."

Silvestro Micera, PhD -Scuola Superiore Sant'Anna,Pisa; Ecole Polytechnique Federale de Lausanne, EPFL

"The need for further standardization in the domain of neurotechnology is clear, on three different levels:

1. First, in the domain of neurotechnology research reporting, we need to provide sufficient information about the technical details of our systems and studies in a very repeatable and consistent way, to allow other groups to replicate our experiments and to compare different approaches.
2. Second, we need to standardize the methods used to validate the efficacy of different approaches, for a clear comparison of results and advancement of neuroscientific understanding and neurotechnology.
3. Third, we need to allow different 'building blocks' developed by different research groups and companies to be easily integrated, to provide more flexible solutions for patients and other end users."

Dennis McBride, PhD – Chief Strategy Officer/Sr. Scientist, NeuroRx Pharmaceutical; Chief Strategy Officer, Source America

"Standards of course facilitate technical communication within and among stakeholders—from basic research to product sales. The establishment of standards at the earliest phase of basic research is vital because this sets the stage and the fundamental, technical taxonomies for disciplined communication as the science/technology progresses. The ultimate value to the public stakeholder is that standards--from the basic research taxonomy/dictionary all the way through to introduction of useful technology, enable 'product manufacturers' to compete within definable 'lanes.' Competition tends to increase quality and affordability; but it also provides the types of cross-technology interface specifications that encourage 'add-on' product development and support."

Jean-Louis Divoux – Expert Adviser, Active Implantable Medical Devices (AIMD)

"On behalf of my company (MXM, the fourth insignificant French cochlear implant manufacturer), from 1998 to 2009, I participated in writing the EN 45502-2-3 Standard: Particular requirements for cochlear and auditory brainstem implant systems. Yes – it took 11 years to launch this safety standard (!), but nowadays, if you attend a conference dedicated to such particular devices, you will see consensus and real science supporting device safety and efficiency for the benefit of the patients. No more controversies, nor "marketing" arguments, or endless discussions on constant current versus voltage configurations for electrostimulation – just experts in their specialties including medical and biotechnologies, electronics, mechanics, and public health, all exchanging, comparing, and sharing their experiences with a single aim: to converge to a broad common agreement and harmony, and settle as foundations topics that have become mutually evident and indisputable, to go ahead and take up further challenges.

In the end, standards are some of those tools that you cannot work without once you have grown accustomed to them. Their development often appears to be a long process, but I have witnessed that it pays, and if done well, will just appear 'natural' for future generations and users."

Carole C. Carey, Consultant, C3-Carey Consultants, LLC – Regulatory Challenge and Opportunity

"Medical devices are highly regulated products. One of the challenges that manufacturers face, particularly multinational firms, is overcoming complex government regulatory review of new devices. A lengthy market approval process can impede innovation and delay the availability of innovative devices to benefit patients. Regulatory bodies across international jurisdictions recognize that established industry consensus standards help simplify the process of designing, developing, testing and manufacturing new technologies. Regulators support the use of harmonized standards as one of the regulatory tools that augment the supervision and management of medical products. However, the development of device standards is lagging behind, such as in the field of neurotechnology involving brain-machine interfaces, neurostimulation, neuroprosthetics, neuromonitoring, and implanted devices. These devices not only augment nervous system activity, but expand its potentials to benefit people with severe disabilities, enabling paralyzed patients achieve direct brain control of mobility-assistive devices and interact with their environment, for example. The development of international, consensus standards should move forward to catch up with technology innovations."

Statement from BIOS

At BIOS, a full-stack neural interface company, we see the development of open standards for neurotechnology as a vitally important step in establishing a more sustainable market for advanced neurotechnologies. We believe that by collaborating in this effort, we can play our part in enabling the field to move from purely the range of technical and scientific discussions prevalent today, to some of the under-addressed applied neurotechnology questions such as "How do we provide better overall healthcare to the patient with neurotechnology?" We also believe that leading open standards for the commercial ecosystem and supply chain can pave the path to the faster adoption of our own innovations and also make it possible for faster iteration and more mutual innovation when we collaborate with others. Finally, we see standardization as an enabling factor in increasing the accessibility, availability, and affordability of such a life-changing and revolutionary set of technologies.

One of the most powerful technological open standards of the information era has been the communication protocols that power the Internet. These have ultimately underpinned a rich and diverse commercial ecosystem that has spawned many generations of successful companies and driven an ever-increasing pace of technology development. With the emergence of neurotechnology we will soon have the opportunity to interact with "the Internet of the body." This will enable us to build applications that will benefit society: new type of therapies, healthcare reimagined, a new way of interacting with technology, and many more. Open standards allow everyone to use the same interfacing protocols, enable us to build safer systems and accelerate the creation of the valuable applications that benefit humanity.

Blair Lock—CEO COAPT. Case study on end-effectors: Upper limb neuroprosthetics

"COAPT is a neurotechnological company founded on focused and dedicated research to deliver modern myoelectric control for the benefit of users and clinicians alike."

COAPT provides a control solution that employs advanced pattern recognition algorithms that predict motor commands from electromyography (EMG). Their devices are marketed to help enhance the control of upper limb prosthesis for amputees. We interviewed COAPT CEO Blair Lock, to learn about their experiences and challenges on how they developed their device, particularly on the aspect that their device is compatible with multiple upper limb prosthetic devices on the market. The following summary is based on a phone interview that Akshay Sujatha Ravindran from the University of Houston's laboratory for noninvasive brain-machine interface systems did with the CEO Blair Lock.

The most recent standardization efforts in communicating with upper limb prosthesis

The perception that is prevalent in many cases is that conventional prosthetic devices have their own communication protocol and their own physical interface. However, most of the traditional control is performed in an analog fashion and is not too complicated to work with. Everyone is excited about the world of robotic prosthetics; however, most of these are still archaic in their design of the electrical connections and how they communicate with one another.

How difficult it is to work with existing communication protocols?

A major part in making different devices become compatible with one another is understanding how each component works well with others. Typically, this problem can be addressed in multiple ways depending on the level of complexity and collaborations with third party device companies. In devices belonging to the lower end of the complexity scale, they do not require either side to do much work/collaboration, as its operation is relatively well understood. For devices belonging to the higher end of the scale, having a collaboration helps. Even though some of them have different communication protocols, pretty much all of them use existing digital standards and having these collaborations helps modify the system to run the API and ensuring that they allow COAPT's system to communicate with theirs using a polished API (see Figure 14).

This does not necessarily mean that it is a straightforward plug and play model wherein the two systems can be interfaced without any modifications. On the clinician's side, there is typically a need for slight modifications to be made to the prosthetic device, which do not fall under engineering level modifications and can be performed by the clinicians themselves. The interface from the COAPT company comes pre-configured from their office ready to communicate with the device of interest.

What is the willingness of prosthetic companies to disclose the control strategies with COAPT?

An extensive 30-year record of conducting clinical trials and academic publications have showcased their value before the prosthetic companies and has aided them in securing sufficient scientific backing. This encouraged the companies to permit COAPT to indulge in engineering their devices to make them compatible, after following different Non-Disclosure agreements or other legal arrangements.

A common control paradigm is not a single ended question. Companies might not necessarily be interested in adopting standards mainly due to economic factors. Making their devices interoperate with others would de-verticalize the market, which does not really improve their business. That is, limiting interoperability restricts buyers from seeking device components from competitors to maintain or upgrade their devices. While interoperability might excite researchers, companies are not necessarily attracted to it.

View on standardizing neurotechnology?

According to COAPT CEO Blair Lock, prosthetics is not yet a domain that is in dire straits without standardization. Unlike other larger-volume consumer industries, this field of neurotechnology is not yet advanced or “smart” enough to procure standardization. Given the current state of technology, the lack of standards does not currently hinder endpoint users. They can work with clinicians and prosthetists to source the required components from the respective manufacturers and assemble these components together.

Discussion

Consideration of standards, modularity and interoperability among the prosthetic device industry can be challenged by economic factors, level of collaboration among device makers, technology complexity, and the market size. While researchers and emerging companies may benefit from standards, modularity, and interoperability for the design of new devices with advanced functions, current device companies may feel the need for ‘de-verticalizing’ the market, which might affect their market.

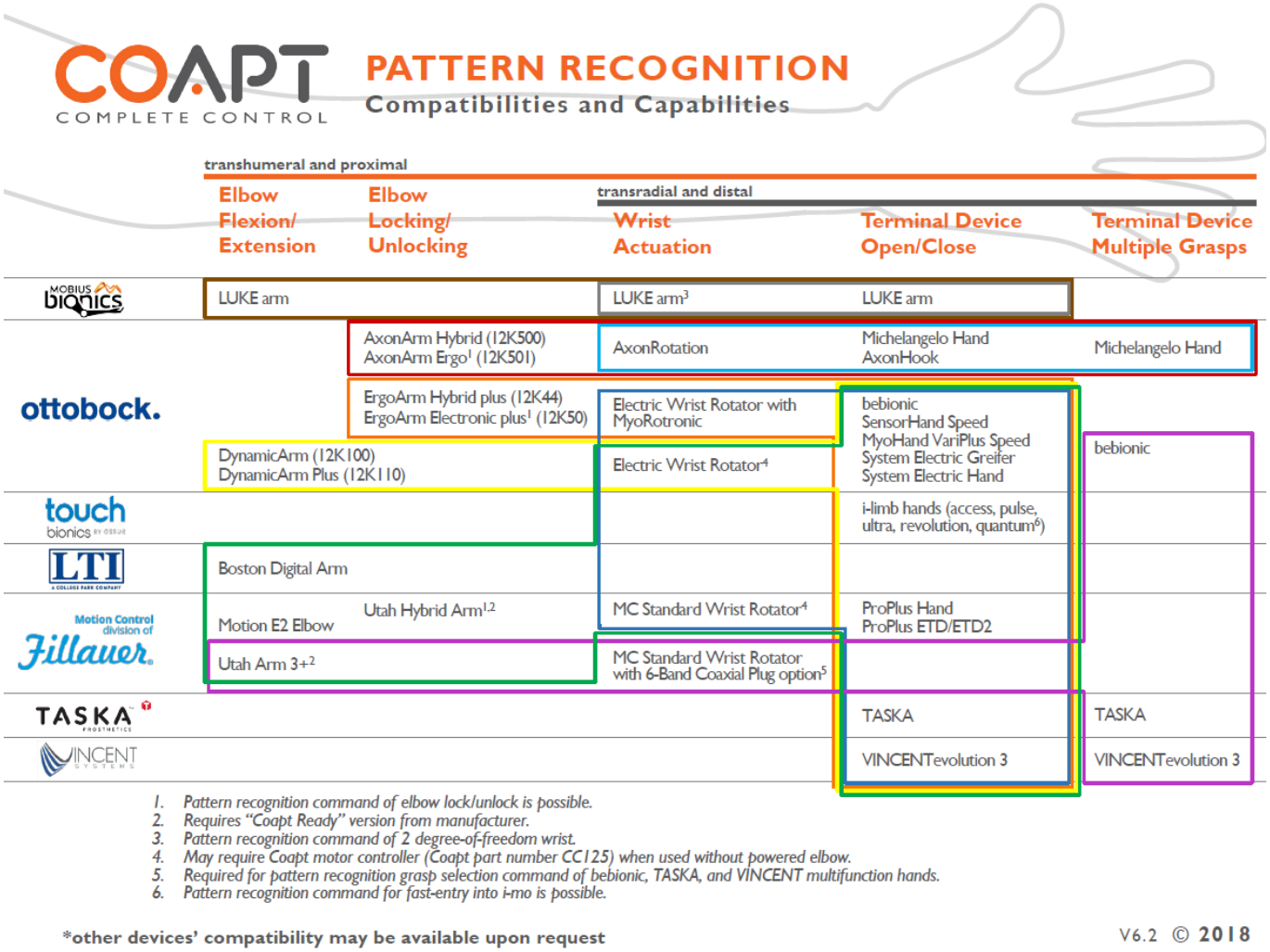

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Figure 14—Configurations compatible with COAPT COMPLETE CONTROL system (Source)

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