DISCUSSION PAPER

Neurotechnology and Noninvasive Neuromodulation

Case Study for Understanding and Anticipating Emerging Science and Technology

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This discussion paper is one in a series of three that present case studies of emerging science and technology applications in order to better understand, anticipate, and develop governance for the development of similar emerging technologies, with attention to their potential societal, ethical, legal, and health-related impacts. These case studies were developed by members, academic collaborators, and staff of the National Academy of Medicine's Committee on Emerging Science, Technology, and Innovation in Health and Medicine (CESTI) and should be used to spur conversation and further investigation into the potential impacts of emerging technologies. Read more about CESTI at https://nam.edu/programs/committee-on-emerging-science-technology-and-innovation-in-health-and-medicine.

Introduction

This case study was developed as one of a set of three studies, focusing on somewhat mature but rapidly evolving technologies. These case studies are intended to draw out lessons for the development of a cross-sectoral governance framework for emerging technologies in health and medicine. The focus of the case studies is the governance ecosystem in the United States, though where appropriate, the international landscape is included to provide context. Each of these case studies:

- describes how governance of the technology has developed within and across sectors and how it has succeeded, created challenges, or fallen down;
- outlines ethical, legal, and social issues that arise within and across sectors;
- considers a multitude of factors (market incentives, intellectual property, etc.) that shape the evolution of emerging technologies; and
- identifies key stakeholders.

Each case study begins with two short vignettes designed to highlight and make concrete a subset of the ethical issues raised by the case (see *Box 1* and *Box 2*). These vignettes are not intended to be comprehensive but rather to provide a sense of the kinds of ethical issues being raised today by the technology in question.

The cases are structured by a set of guiding questions, outlined subsequently. These questions are followed by the historical context for the case to allow for clearer understanding of the trajectory and impact of the technology over time and the current status (status quo) of the technology. The bulk of the case consists of a cross-sectoral analysis organized according to the following sectors: academia, health care/nonprofit, government, private sector, and volunteer/consumer. Of note, no system of dividing up the world will be perfect—there will inevitably be overlap and imperfect fits. For example, "government" could be broken into many categories, including international, national, tribal, sovereign, regional, state, city, civilian, or military. The

BOX 1 | Neuromodulation Vignette 1

In 2022, a 67 year old Australian woman, Robyn, was prescribed transcranial direct current stimulation (tDCS) by her physician in Sydney to treat her major depression and was finding relief of her symptoms with this therapy. Under the close supervision of her psychiatrist, at the doctor's office, she received a course of low intensity (2 milliampere) tDCS delivered to her left dorsolateral prefrontal cortex (DLPFC) for 20 minutes each weekday for 4 weeks. Her treatment has the approval of Australia's Therapeutic Goods Administration (TGA) and is covered by her private insurance (tDCS is not covered by public insurance in Australia). Due to a new job opportunity, she emigrated to the United States. Given the as yet inconclusive efficacy data available for the use of tDCS in the treatment of depression, the U.S. Food and Drug Administration (FDA) has not approved the device for clinical use, and so Robyn no longer has access to clinical tDCS. Robyn cannot afford to travel home to Australia for periodic treatment, so she begins to look for other ways to access treatment. A brief search online identifies several tDCS devices that are commercially available, direct to consumer, in the United States. She orders a device, marketed as a wellness aid, that she thinks most closely resembles the one with which her physician was treating her. $250 and 1 week later, she begins using the device at home, trying her best to remember and replicate the treatment dosage, location on her head, and settings she received from her psychiatrist.

Potential benefits: Access to mental health care, affordability, and convenience

Potential concerns: Lack of medical supervision, commercial rather than clinical-grade device, potential displacement of medically supervised care, and safety

BOX 2 | Neuromodulation Vignette 2

In 2020, like much of the rest of the world, Liam was at home, keeping himself and his family as safe as possible from the COVID-19 pandemic. Liam is 14 years old and in the ninth grade, attending school remotely. His little brother and both his parents are also schooling and working from home. When Liam's school day ends at 3 pm, he switches from his school laptop to his game console. For his birthday, his parents got him a tDCS device to use for gaming. The device is marketed as a way to improve attention and focus, which Liam really needs to help him complete the game he's currently playing. He feels like the device helps him not only with gaming but also with his demanding workload at school and with violin practice and performance, so he uses it once or twice a day to try to maintain his edge. His little brother, who is in third grade and struggles with attention deficit and hyperactivity disorder (ADHD), uses it occasionally as well. The device, which is not regulated by the FDA, is intended to be used by adults once a day for 20–30 minutes.

Potential benefits: Perceived improvements in performance across multiple activities, and potentially improved markers of performance (e.g., grades)

Potential concerns: Unknown risks of chronic use in children, and off-label use

sectoral analysis is further organized into the following domains: science and technology, governance and enforcement, affordability and reimbursement, private companies, and social and ethical considerations. Following the cross-sectoral analysis is a broad, nonsectoral list of additional questions regarding the ethical and societal implications raised by the technology.

The next section of the case is designed to broaden the lens beyond the history and current status of the technology at the center of the case. The "Beyond" section highlights additional technologies in the broad area the focal technology occupies (e.g., neurotechnology), as well as facilitating technologies that can expand the capacity or reach of the focal technology. The "Visioning" section is designed to stretch the imagination to envision the future development of the technology (and society), highlighting potential hopes and fears for one possible evolutionary trajectory that a governance framework should take into account.

Finally, lessons learned from the case are identified—including both the core case and the visioning exercise. These lessons will be used, along with the cases themselves, to help inform the development of a cross-sectoral governance framework, intended to be shaped and guided by a set of overarching principles. This

governance framework will be created by a committee of the National Academies of Sciences, Engineering, and Medicine (https://www.nationalacademies.org/our-work/creating-a-framework-for-emerging-science-technology-and-innovation-in-health-and-medicine).

Case Study: Neurotechnology

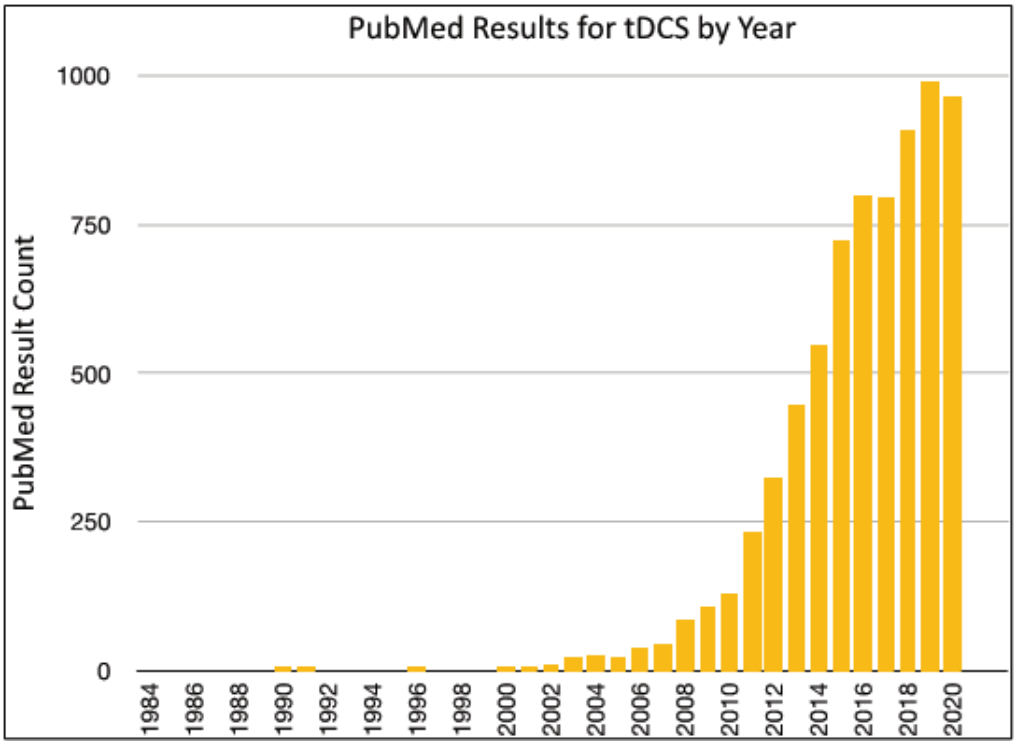
Multiple national-level research projects are under way around the world with the goal of revolutionizing understanding of the human brain, in the same way that the Human Genome Project transformed the understanding of the genome (International Brain Initiative, 2020). Just as the Genome Project has enabled both the reading of genomes and the modification, synthesis, and writing of genomes, the growing and evolving understanding of the brain is now enabling both monitoring and modulation. Neural modulation technologies have the potential to offer significant benefits to individuals and society, including through life-changing treatments and therapies for patients and the potential to mitigate cognitive decline associated with aging among other benefits (e.g., Anderson et al., 2020; Lee et al., 2019; Reinhart and Nguyen, 2019). At the same time, these technologies also raise a new constellation of ethical and societal issues, including questions about personal identity and autonomy, data security, equity, fairness, and legality (NIH, n.d.).

In particular, neural interfaces—frequently used to describe electronic devices that are placed on the outside or inside of the brain or other components of the central and peripheral nervous system to record or stimulate activity—both raise complex questions for society and are increasingly available both clinically and direct to consumer (DTC) in products designed to observe, interpret, and modify human brain function.

Neural interfaces with narrow applications are already in use in health and medicine. For example, deep brain stimulation, which requires surgical implantation, is approved by the FDA to treat patients with conditions such as Parkinson's disease, essential tremor, epilepsy, and obsessive-compulsive disorder and is being studied in the treatment of other disorders of mood, behavior, and thought (Lee et al., 2019). Transcranial magnetic stimulation (TMS) is being used to treat patients with major depressive disorder and obsessive-compulsive disorder and is being studied in the treatment of pain, addiction, post-traumatic stress disorder, traumatic brain injury, and other conditions (Anderson et al., 2020). External, wearable interfaces are being studied and in some cases being used clinically in people with major depression, chronic pain, stroke and spinal cord injury rehabilitation, and epilepsy management (Avila et al., 2021; Brinkmann et al., 2021; Pedrelli et al., 2020; James et al., 2018).

Transcranial direct current stimulation (tDCS) is a noninvasive neuromodulation technology that is portable, relatively inexpensive, and relatively safe when used within safety guidelines (Elsner et al., 2020). Though the technology has been around for decades, interest in (see *Figure 1*) and availability of the technology have dramatically increased over the last decade. tDCS is being increasingly used in research on psychiatric disorders,

FIGURE 1 | Increase in PubMed Results for All Journals, Including "tDCS" by Year (search conducted February 19, 2021)



SOURCE: Developed by authors.

cognitive and motor performance, epilepsy, and other health conditions; is being used clinically (primarily for major depression and chronic pain) in a number of countries (e.g., Singapore and Canada); and is available commercially, in modified forms, for consumers motivated by health, wellness, and enhancement applications. This availability persists despite the controversy that remains regarding the mechanism of action of tDCS and the fact that the evidence base to support clinical translation remains limited (Regner et al., 2018; Kekic et al., 2016). This case study's focus on tDCS was driven primarily by two factors: first, there is both a history of use and governance that can be traced and learned from, and there is promise of continuing evolution of the technology going forward; and second, this technology has had a clear impact across at least three sectors, with significant footprints in research (academic sector), clinical care (health care sector), and DTC treatments (volunteer/consumer sector).

Guiding Questions (derived from Global Neuroethics Summit Delegates, 2018; Mathews, 2017)

The following guiding questions were used to frame and develop this case study.

- **Historical context:** What are the key scientific antecedents and ethics touchstones?
- **Status quo:** What are the key questions, research areas, and products/applications today?
- **Cross-sectoral footprint:** Which individuals, groups, and institutions have an interest or role in emerging biomedical technology?
- **Ethical and societal implications:** What is morally at stake? What are the sources of ethical controversy? Does this technology or application raise different and unique equity concerns?

Additional guiding questions to consider include the following:

- **Key assumptions around technology:** What are the key assumptions of both the scientists around the technology and the other stakeholders that may impede communication and understanding or illuminate attitudes?
- **International context and relevant international comparisons:** How are the technology and associated ethics and governance landscape evolving internationally?
- **Legal and regulatory landscape:** What are the laws and policies that currently apply, and what are the holes or challenges in current oversight?
- **Social goals of the research:** What are the goals that are oriented toward improving the human condition? Are there other goals?

Historical Context

What are the key scientific antecedents and ethics touchstones?

tDCS was first used in research in nonhuman animals and has been studied in humans since at least the mid-1960s, though interest in the technology rapidly increased about 10 years ago, apparently due to improvements in the technology, including the necessary microprocessors and batteries, associated decreases in cost, and improvements in parameter control (Esmaeilpour et al., 2017; Sarmiento et al., 2016).

While tDCS is arguably less risky than earlier, significantly more invasive attempts at neuromodulation, it is important when discussing any brain intervention, and particularly those intended to treat patients with a psychiatric disease or for use in other historically underserved or marginalized populations, such as children and those with dementia, to be reminded of the problematic history of psychosurgery. While there was both a scientific rationale and claims of benefit in early studies of psychosurgery, lobotomy surgery, like other emerging technologies before and after it, was adopted more rapidly and broadly than justified by the available evidence of safety and efficacy (at least 20,000 cases in the United States by 1950), including increased use following World War II, in an effort to relieve psychiatric conditions among veterans (Pressman, 1998; Valenstein, 1986). As a result, significant harm was caused to many historically underserved and marginalized populations, for what subsequent research suggested was a relatively low probability of benefit, given the risks posed by the surgery.

Furthermore, problematic use of psychosurgery did not stop following the lobotomy surgeries popularized in the United States by Walter Freeman and James Watts in the 1930s to the 1950s. While interest and use waned by the late 1950s, following reports of poor outcomes and as pharmacologic options became available, a resurgence in interest was prompted by improved understanding of the brain and development of more targeted psychosurgery techniques in the late 1960s and early 1970s (Federal Register, 1977). At this time, public and professional concern was sparked in part by suggestions that a contributor to the social unrest and uprisings of the 1960s was underlying brain abnormalities that predisposed some urban "slum dwellers" to violence and by reports that psychosurgery was being done not only on those with psychiatric disease (most of whom were women) but also on the young, including African American children (Kucharski, 1984; Breggin, 1982; Federal Register, 1977; Mark et al., 1967). The U.S. Congress, the National Institutes of Health, and the American Psychiatric Association all focused their attention on psychosurgery, leading to a series of hearings, guidelines, and reports, including one by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, emphasizing the ethical aspects of this problem (Federal Register, 1977).

Status Quo

What are the key questions, research areas, and products or applications today?

tDCS is a noninvasive neuromodulation technology that uses a constant, low-intensity current run through two or more electrodes placed on the scalp. tDCS is thought to increase (positive/anodal tDCS) or decrease (negative/cathodal tDCS) neuronal excitability, though there is still debate about mechanism. Specifically, there remains controversy as to whether the actions of tDCS are due to direct effects on the brain or due to indirect effects resulting from stimulating nerves and muscles in the scalp (Nikolin et al., 2018). The selection of a biologically inactive and plausible sham condition also remains a matter of debate, with some studies suggesting biological effects from sham conditions that were thought to be inert (Nikolin et al., 2018). The data regarding clinical utility are also inconsistent. That said, tDCS is portable and wearable, relatively safe and inexpensive, and appears to have somewhat durable effects (Wang and Voss, 2015; Snowball et al., 2013). There has been rapid growth in interest and use in research and in the DTC market over the past 10 years.

tDCS is currently used in research (e.g., depression and other disorders of mood, thought, and behavior, as well as cognitive performance). However, there is considerable variability in research results, with some studies demonstrating modest effect and others demonstrating negligible or negative effects (Palm et al., 2016a). tDCS has been used to study diverse topics including learning; cognitive performance; physical performance; perception; traumatic brain injury; depression; other disorders of mood, thought, and behavior; and aphasia (Marques and Scanavino, 2020; Kekic et al., 2016; Okano et al., 2015; Monti et al., 2013; Clark et al., 2012; Reis et al., 2009). In any given area of investigation and particularly in translational research on human disease treatment, studies can be difficult to compare due to considerable heterogeneity in study design (e.g., study population, stimulation target, stimulation parameters). These differences, coupled with the small sample size of most studies and human diversity (including neurodiversity), contribute to the variability of the evidence produced. Several studies have examined the safety of tDCS for children, and systemic reviews of these studies indicate that the side effects of tDCS in children are typically mild and transient and that the technology is safe for use in the short-term (Palm et al., 2016b; Krishnan et al., 2015). However, the long-term effects of tDCS in developing brains remain unknown, and relatively less work has been done to date focusing on children (Davis, 2014). Overall, additional study is needed to understand the mechanism of action of tDCS and to develop the evidence base to support clinical translation.

Currently, tDCS has some limited clinical use globally, primarily in treatment of major depression and chronic pain (Fregni et al., 2020; Lafaucheur et al., 2017). The evidence supporting these applications is highly variable and generally based on uncontrolled studies of small numbers of people (O'Connell et al., 2018). Major depression is the psychiatric disease most studied with tDCS, followed by schizophrenia and substance use disorders. Obsessive compulsive disorder, anxiety disorder, and anorexia have also been studied, but to lesser degrees (Kekic et al., 2016). Clinical use of certain tDCS devices is approved in Australia, though approval specifies that this "should only be undertaken following the recommendation of a psychologist, with close monitoring by a healthcare practitioner" (Australian Government, n.d.) Furthermore, this approval is not without controversy, as the Royal Australian and New Zealand College of Psychiatrists issued a memorandum highlighting that there is emerging—but not conclusive—evidence for efficacy of tDCS use in the treatment of depression, and emphasizing that, "[f]or depression tDCS should be given within research trials or if used clinically using approaches that are consistent with available evidence and with clinical governance in place, including arrangements for full audit and review of clinical outcomes of all patients. Patients should be informed that the evidence base for its use in depression is currently limited" (RANZCP, 2022; Loo et al., 2018, 2012, 2010; Al-Kaysi et al., 2017; Brunoni et al., 2017, 2016, 2013; Lafaucheur et al., 2017; NICE, 2015). Treatment with tDCS is not currently covered by the public health care system in Australia.

Clinical use of tDCS in the treatment of depression and fibromyalgia has also been approved by Singapore's Health Science Authority (HSA). The HSA assessed the clinical evidence for efficacy for such therapies to be "of moderate level," including evidence of long-term durability of therapy (personal communication, 2022). At this time, the HSA appears to have judged that the benefits outweigh the risks of the treatment. The HSA does conduct post-market surveillance to monitor clinical performance and is prepared to modify guidance if justified by the resulting data. To date, there is no coordinated global governance of this technology.

There is optimism in the field that with improved understanding of disease and individualized targeting, efficacy will improve (Jog et al., 2019). Optimization of treatment effects may require a combination of neuromodulation with pharmaceutical and behavioral interventions (NASEM, 2015). One crosscutting gap in knowledge relates to the long-term effects of tDCS use.

Of note, the COVID-19 pandemic may facilitate more widespread use of tDCS, due to its favorable risk profile and the ability for the treatment to be administered at home under the direction and observation of a physician via telemedicine. In fact, in May 2020, the FDA approved an Investigational Device Exception (IDE) supplemental protocol study submitted by Neuroelectrics, permitting a trial of home treatment with tDCS for patients with major depression whose prior noninvasive brain

stimulation treatment (repetitive transcranial magnetic stimulation [rTMS] or electroconvulsive therapy [ECT]) was unavailable due to the pandemic (Serra, 2020).

There is a small but growing body of literature on the potential clinical applications of the technology for use in children. Proposed clinical applications of tDCS in children include treatment of ADHD, autism spectrum disorders, childhood-onset schizophrenia, epilepsy, dyslexia, cerebral palsy, and dystonia and other movement disorders. Research findings are mixed on many of these conditions, although a systematic review of the literature indicates that tDCS may be effective at treating ADHD, cerebral palsy, epilepsy, and other neurological conditions (Breitling et al., 2020; Gillick et al., 2018; Kirton et al., 2017; Soff et al., 2017; Bandeira et al., 2016; Palm et al., 2016b; Grecco et al., 2014; Auvichayapat et al., 2013). Evidence of the effectiveness of tDCS for treating childhood psychiatric conditions such as schizophrenia is lacking (Muszkat et al., 2016). Studies in children have been criticized for their design, as there is a distinct lack of randomized, sham-controlled trials in pediatric populations, in part due to the wide range of ethical concerns raised by performing tDCS research on children, including the uncertain risk/benefit profile (Sierawska et al., 2019; Hameed et al., 2017).

Overall, large, randomized, controlled trials with more diverse groups of patients are needed to improve the evidence base.

There is also a robust DTC market for tDCS devices (see *Table 1*), which are marketed largely for wellness and enhancement applications but are used by consumers with a variety of goals, including the treatment of health conditions.

TABLE 1 | Selection of Research, Clinical, and DTC Applications for tDCS Devices

Research (Select Examples of Ongoing Trials)		
Where	**Description**	**Condition**
Brazil	Effects of tDCS for the treatment of refractory epilepsy (NLM, 2020)	Epilepsy
EU—Horizon 2020 Funded Project	Transcranial brain stimulation as innovative therapy for chronic pediatric neuropsychiatric disorder—STIPED	Chronic pediatric neuropsychiatric disorders such as ADHD and autism spectrum disorder (ASD)
Germany	Augmentation of cognitive behavioral therapy (CBT) with tDCS in major depressive disorder (Bajbouj et al., 2018)	Major depressive disorder (MDD)
United States	tDCS neuromodulation of executive function across neuropsychiatric populations	Neuropsychiatric disorders (traumatic brain injury, MDD, bipolar disorder, schizophrenia, ADHD, borderline personality disorder, and substance use disorder)
Clinical (Select Examples)		
Where	**Applications**	**Description**
Canada	Chronic pain	Health Canada has approved tDCS for use in chronic pain
Australia	Major depression, pain	Therapeutic Goods Administration (TGA) has approved tDCS devices for use in major depression and pain in adults
Singapore	Major depression and fibromyalgia	Singapore's Health Sciences Authority (HSA) has approved some tDCS products for use in major depression and fibromyalgia
Brazil	Pain and depression	Brazil's National Health Surveillance Agency (ANVISA) has approved some tDCS devices for pain and depression
Europe	Pain	Within the European Union, several countries permit off-label use of tDCS, including Italy, France, and Germany.
Direct to Consumer Devices (Select Examples)		
Product	**Price**	**Manufacturer Description**
Halo Sport 2	$399	Halo Sport is a brain stimulator that helps you develop muscle memory faster.

Flow	€459	The Flow headset is the first portable tDCS device, medically approved for home use in the United Kingdom and the European Union. Because of its unique safety system and user-friendly design, the Flow tDCS device offers you the possibility to recover from depression in the comfort of your own home. The brain stimulation technique is backed by more than 10 double-blind, placebo controlled, clinical trials, making this tDCS headset well-trusted by experts in the field of psychiatry.
LIFTiD neurostimulation	$149	A new hi-tech consumer product, powered by tDCS that will dramatically change the way we live. Using LIFTiD neurostimulation for 20 minutes a day trains the brain to maximize attention, focus, and alertness, thus putting the LIFTiD user in the right mindset to accomplish tasks and perform at a higher level. Studies show that tDCS alters brain function by increasing blood flow, enhancing neurotransmitter release and activating neurons.
BrainDriver	$139	TheBrainDriver.com tDCS v2.1. Ships Worldwide. Safety features built-in. Professional tDCS System. Digital Output and precision controls. Comes ready-to-use out of the box with battery and all accessories. Your package includes TheBrainDriver tDCS main unit with user-friendly safety features: 20- and 30-minute timer backlit digital display for nighttime use.
ActivaDose tDCS device starter kit	$375	Easy to use and simple to set up, the Activadose is the only FDA cleared device available for tDCS. This tDCS device is recommended by physicians and approved by Institutional Review Boards for tDCS trials. The Activadose is a medical grade device that has all the necessary features you look for in a tDCS Device. Get started with tDCS today.
PlatoWork brain stimulator	$395	Improve your memory, focus, and creativity. The PlatoWork headset is a plug and play device designed to make neurostimulation as easy as possible. Simply put on the PlatoWork headset, select stimulation mode in the app, and start working. By increasing activity in specific areas of the brain, PlatoWork allows you to enter the mindset you need to solve a task.
Focus V3 tES Device	$399.99	The new and improved tES device by Focus with tDCS, tACS, tPCS, tRNS, and tRCS waveforms as well as blind and double blind placebo (sham) modes. Easy to use interface consisting of just a simple yet unique 4-way joystick. Built-in LCD screen shows device settings. Small and portable, the V3 has a rechargeable battery and includes the necessary accessories to get started with tDCS right out of the box. Grab a Focus V3 to fully customize your neuromodulation sessions. The Focus V3 is CE marked.
Apex Type A tDCS device	$149.99	The ApeX Type A 18V—Ultimate Bundle is a great way to get started with tDCS as quickly as possible. It includes a complete set of accessories for those who want get going right out of the box. Analog design means you can control the current, current ramp-up, and duration manually.
Focus Go Flow 4 mA tDCS device	$244	Small, handheld, easy to use tDCS brain stimulator with ramp-up and ramp-down functionality and a 1 mA to 4 mA intensity range and duration range of 5 to 35 minutes. Includes 0.75Hz sotDCS mode—slow oscillating tDCS.

SOURCE: Developed by authors.

Cross-Sectoral Footprint

The cross-sectoral analysis is structured according to sectors (academia, health care, private sector, government, and volunteer/consumer) (see *Figure 2*) and domains (science and technology, governance and enforcement, end-user affordability and insurance reimbursement [affordability and reimbursement], private companies, and social and ethical considerations). The sectors described subsequently are intended to be sufficiently broad to encompass a number of individuals, groups, and institutions that have an interest or role in tDCS. Health care is the primary nonprofit actor of interest, and so in this structure, "health care" has replaced "nonprofit," though other nonprofit actors may have a role in this and other emerging technologies, and, of course, not all health care institutions are nonprofits.

Today, neuromodulation technologies are researched, developed, and promoted by a scientific-industrial complex largely driven by market-oriented goals. The development of various forms of tDCS may be altered by differing intellectual property regimes. This larger ecosystem is also embedded in a broad geopolitical context, in which the political and the economic are deeply intertwined, shaping national and regional investment and regulation. The political economy of emerging technologies involves and affects not only global markets and regulatory systems across different levels of government but also nonstate actors and international governance bodies. Individuals and societies subsequently adopt emerging technologies, adjusting their own values, attitudes, and norms as necessary, even as these technologies begin to shape the environments where they are deployed or adopted. Furthermore, individual and collective interests may change as the "hype cycle" of an emerging technology evolves (Gartner, 2022). Stakeholders in this process may include scientific and technological researchers, business firms and industry associations, government officials, civil society groups, worker safety groups, privacy advocates, and environmental protection groups, as well as economic and social justice–focused stakeholders (Marchant et al., 2014).

This intricate ecosystem of stakeholders and interests may be further complicated by the simultaneous introduction of other technologies and platforms with different constellations of ethical issues, modes of governance, and political economy contexts. Subsequently, this ecosystem is disaggregated and organized for ease of presentation. It is important to keep in mind that there are entanglements and feedback loops between and among the different sectors, such that pulling on a single thread in one sector often affects multiple areas and actors across the broader ecosystem.

Cross-Sectoral Analysis

Academia

For the purposes of this case study, the primary actors within the academic sector are those conducting basic and translational research on tDCS and scholars working in neuroethics or philosophy.

- *Science and technology*: tDCS in humans has been explored in the research context since at least the mid-1980s. Topics of study include learning, perception, and cognitive and physical performance. The focus of translational research has included depression; compulsive sexual behavior; other disorders of mood, thought, and behavior; chronic pain; and seizure disorder (Marques and Scanavino, 2020; Kekic et al., 2016). There are also studies under way seeking to define mechanisms of action at the circuit and cellular level (Yamada and Sumiyoshi, 2021; Pelletier and Cicchetti, 2015).
- *Governance and enforcement:* Within the research context, governance is primarily through institutional human

FIGURE 2 | Sectors for Cross-Sectoral Analysis

SOURCE: Developed by authors.

subject research institutional review boards (IRBs) and research ethics boards (REBs), research funding bodies, academic publication standards, and scientific and professional societies (i.e., self-regulation).
- *Affordability and reimbursement:* N/A
- *Private companies:* Academic–industry research partnerships, including industry-funded clinical trials, are involved in this space. The availability and enforceability of intellectual property may further affect the relationship among participants in such partnerships.
- *Social and ethical considerations:* There has been considerable academic research and analysis related to ethical issues raised by neuroscience and neurotechnologies in particular, including implications for personal identity, autonomy, agency, human rights, and privacy and confidentiality (Eberwine and Kahn, 2020). This literature both responds to these technological advances and tries to anticipate downstream concerns.

Health Care

Given the focus of CESTI on health and medicine, for the purpose of this case study, the primary actors within the nonprofit sector with applicability to this discussion are those involved in health care.

- *Science and technology:* As noted previously, translational research is under way, though data on efficacy are limited and highly variable. There are no standard treatment protocols, and long-term safety data are unavailable. Much of the clinical use appears to depend on the perceived favorable risk profile of the technology.
- *Governance and enforcement:* To date, the FDA has not approved a tDCS device for medical use. However, the FDA did recently approve an IDE supplemental protocol study submitted by Neuroelectrics, permitting a trial of home treatment with tDCS for patients with major depression whose prior noninvasive brain stimulation treatment (repetitive transcranial magnetic stimulation [rTMS] or electroconvulsive therapy [ECT]) was unavailable due to the COVID-19 pandemic (Serra, 2020). Health Canada has approved tDCS for use in chronic pain. In Australia, the TGA has approved tDCS devices for use in major depression in adults. Singapore's HSA has approved some tDCS products for use in major depression and fibromyalgia. The HSA does conduct post-market surveillance and would make any necessary adjustments in approval should there be evidence of, for example, safety concerns. In Europe, some tDCS products have received the Conformité Européenne (CE) mark, indicating that the products conform with health, safety, and environmental protection standards for products sold within the European Economic Area, though this is not the equivalent of receiving FDA approval in the United States or National Institute for Health and Care Excellence (NICE) approval in the United Kingdom (Your Europe, 2022). Within the European Union, several countries permit off-label use of tDCS, including Italy, France, and Germany. At the professional level, as noted above, the Royal Australian and New Zealand College of Psychiatrists issued a memorandum highlighting that there is emerging, but not conclusive, evidence for efficacy of tDCS use in the treatment of depression, and emphasizing that, "[f]or depression tDCS should be given within research trials or if used clinically using approaches that are consistent with available evidence and with clinical governance in place, including arrangements for full audit and review of clinical outcomes of all patients. Patients should be informed that the evidence base for its use in depression is currently limited" (RANZCP, 2022). Psychiatrists in the United States have also published guidance on appropriate use of the technology (Zandvakili et al., 2019).
- *Affordability and reimbursement:* Even among those countries where tDCS is approved for clinical use, there does not appear to be health insurance coverage under public funding schemes.
- *Private companies:* For-profit health care (e.g., private clinics) and device company lobbyists may have a role here, for example, providing on-site treatment with tDCS devices in stand-alone clinics.
- *Social and ethical considerations:* There are concerns about tDCS efficacy, long-term safety, affordability, risk/benefit balance, and use in vulnerable populations, particularly children and individuals with mental illness.

Private Sector

For the purposes of this case study, the primary actors within the private sector are those developing clinical-grade devices, those involved in the DTC market, and those who might use tDCS to, for example, enhance the focus and performance of their employees.

- *Science and technology:* There are currently many DTC tDCS products on the market internationally (see *Table 1*). Devices are generally marketed for wellness and enhancement or performance improvement applications.
- *Governance and enforcement:* Currently, there appears to be little to no regulation of DTC tDCS globally, though there has been limited involvement by the FDA in the United States (Wexler, 2015). Wexler (2015) argues that within the United States, despite the absence of FDA approval, there is nonetheless a comprehensive regulatory framework for tDCS, involving the FDA, the Federal Trade Commission (FTC), the Consumer Product Safety Commission (CPSC), the Federal Communications Commission (FCC), state regulators, and further soft governance through the market (Wexler, 2015). The European Union

will begin regulating tDCS devices under its Medical Device Regulations, originally scheduled to go into effect at the end of May 2020, but delayed due to the COVID-19 pandemic (EU, 2017). The private sector is also governed and shaped by its ability to secure funding and by investors, in the case of publicly traded companies. Insofar as the devices are used in the workplace, the Occupational Safety and Health Administration (OSHA) would also presumably have an interest. In addition, intellectual property (IP) in this area may affect the attractiveness of pursuing and marketing certain devices, as has been seen for other neurostimulating devices, for instance, Nevro's Spinal Cord Stimulator system (U.S. Court of Appeals, 2020). As with other neurostimulating medical devices, the relative simplicity of the devices makes patent protection difficult; the private sector may be encouraged to seek IP protection through other means—such as trade secrecy—although the ease with which such devices can be reversed engineered makes such alternatives difficult.

- *Affordability and reimbursement:* DTC devices range in cost from approximately $30 for a no-frills self-assembly kit to around $400 for a high-end product.
- *Private companies:* There are significant market incentives for individual companies, given an increasing interest in personal wellness, additional focus on using personal data to improve one's self, and a thriving gaming industry in which players are often willing to go to great lengths for an edge, for example through increased focus and attention. However, there is skepticism among some investors due to insufficient efficacy data, a one-time purchase versus subscription payment model, and consumer fall-off (purchasers get bored after a few months and discontinue use). In addition, difficulties in IP for tDCS devices may make "franchising" of certain tDCS models—that is, the branding and marketing of a device by a single manufacturer—difficult, since the branded device can be readily copied and sold by others, eroding the market for (and therefore the incentive to develop and produce) the branded device.
- *Social and ethical considerations:* There are significant concerns about safety, inappropriate market practices, excessive hype, off-label uses, and conflicts of interest.

Government

For the purposes of this case study, the primary actors within the government sector are those involved in health product regulation, public insurance coverage, and potential military and security applications.

- *Science and technology:* There has been interest both from military leadership and individual members of the military in the use of tDCS for focus and performance enhancement. Military interest is primarily in enhancement (rather than health) applications, but the military is an important driver of research and development. In 2016, the Defense Advanced Research Projects Agency (DARPA) launched the Targeted Neuroplasticity Training (TNT) program "to advance the pace and effectiveness of a specific kind of learning—cognitive skills training—through the precise activation of peripheral nerves that can in turn promote and strengthen neuronal connections in the brain. TNT will pursue development of a platform technology to enhance learning of a wide range of cognitive skills, with a goal of reducing the cost and duration of the Defense Department's extensive training regimen, while improving outcomes" (DARPA, 2016).
- *Governance and enforcement:* As noted previously, federal funding agencies; the FDA, FTC, CPSC, FCC; and state regulators are involved to various degrees in regulation, though their roles and standards for approval are different.
- *Affordability and reimbursement:* As noted previously, even among those countries where tDCS is approved for clinical use, there does not appear to be health insurance coverage under public funding schemes.
- *Private companies:* N/A
- *Social and ethical considerations:* Concerns in this sector include coercion, privacy, data sharing and use, personal identity, autonomy, agency, human rights, and standards of evidence.

Volunteer/Consumer

For the purposes of this case study, the primary actors within the volunteer/consumer sector are patients and consumers who might seek out tDCS for treatment or enhancement and the do-it-yourself (DIY) community, which is sharing instructions for building and use on YouTube, Reddit, and elsewhere. It is important to keep in mind that many members of the public nationally and internationally never have the opportunity to be patients or consumers of emerging technologies, and so do not show up in the following analysis. These members of the public may nonetheless be affected by the development, deployment, and use of such technologies, and those impacts should be taken into account.

- *Science and technology:* Relevant actors include patients, caregivers, and individuals advocating for application of this device for treatment of their own or their child's condition, as well as consumers purchasing low-cost kits and higher-end consumer products, and sharing instructions for use on YouTube, Reddit, and elsewhere. Of note, certain aspects of clinical use are difficult to replicate at home. Specifically, the placement of the anode and the cathode on the head and the degree of saline saturation of the electrode pads are important both for efficacy and safety, and these may not be easily replicated by an individual without specialized training. Furthermore, commer-

cially available devices are typically not built to individually target specific brain areas. If the electrodes are put in the wrong location, the device will likely not work and might induce unintended side effects.

- *Governance and enforcement:* There is currently little to no governance (see the governance and enforcement section under "Private Sector"), and there are significant barriers to governance at the level of the consumer, where private individuals purchase and use DTC products at home, or purchase components and build their own devices.
- *Affordability and reimbursement:* Clinical-grade devices are not FDA-approved and are unlikely to be covered by insurance, limiting access only to those who can afford this treatment. DTC devices are affordable for many, with relatively low barriers to access (see *Table 1*).
- *Private companies:* As noted previously, various companies are making low-cost kits available to consumers to feed demand. Higher-end devices are also available, marketed as wellness and performance enhancing devices (see *Table 1*).
- *Social and ethical considerations:* There are significant concerns about safety (e.g., device settings, use duration, long-term effects); therapeutic misconception among consumers; use in children, whose brains are still developing; and use in other vulnerable groups whose members lack the capacity to consent.

Ethical and Societal Implications

What is morally at stake? What are the sources of ethical controversy? Does this technology or application raise different and unique equity concerns?

In outlining the concerns of the authors in terms of the use of this technology, the authors considered the following ethical dimensions, as outlined in the recent National Academies of Sciences, Engineering, and Medicine report, *A Framework for Addressing Ethical Dimensions of Emerging and Innovative Biomedical Technologies: A Synthesis of Relevant National Academies Reports* (NASEM, 2019):

- Promote societal value
- Minimize negative societal impact
- Protect the interests of research participants
- Advance the interests of patients
- Maximize scientific rigor and data quality
- Engage relevant communities
- Ensure oversight and accountability
- Recognize appropriate government and policy roles

It is important to keep in mind that different uses of this technology in different populations and contexts will raise different constellations of issues. For example, the use of tDCS by adults to improve focus while playing video games is quite different than if it is used in prisons to reduce aggression or in children with ADHD in schools. Some of the specific concerns might include the following:

- Is tDCS as currently used safe and effective? What are appropriate standards of evidence for use in different populations? What are the mechanisms to detect device degradation or failure?
- Who has access (and who does not)? Is tDCS affordable? Is it covered by public and private insurance?
- What are appropriate standards for collection, storage, ownership, access, use, and security of device-collected brain and device-use data across sectors?
- What are the legal implications for example, of use of such devices in legal settings, particularly use by law enforcement, the courts, regulatory agencies, and others to mitigate dangerousness or aggression?
- What are the implications of unconsented or coerced/coercive uses of tDCS (e.g., to reduce aggression in prisons or schools, or improve focus in the workplace)?
- What are the implications of remote device control or manipulation?
- What are the implications of the alteration of psychological or behavioral states in ways that could affect personal identity, including both use in healthy individuals and in the treatment of people with disorders of mood, behavior, and thought?
- Do some uses of these technologies change or threaten the understanding of what it means to be human? Are there cultural differences in how these technologies and their effects are perceived and experienced?
- What are the standards for defining neurological health and disease, particularly for psychiatric conditions? How is neurodiversity taken into account, along with the related debates surrounding the term?
- What are appropriate uses of these devices in children and young adults, whose brains (and identities) are still developing? What are appropriate uses in other historically underserved or marginalized populations?
- What are the implications of the use of tDCS in the incidental or intentional enhancement of behavioral, psychological, and/or cognitive performance?

Beyond tDCS

While tDCS was chosen for this case due to its history and its unique cross-sectoral reach, there are many other neurotechnologies in use and in development that raise their own constellation of social, ethical, and governance concerns.

There are a range of other brain–machine interface technologies being used to treat Parkinson's disease and tremor, aid stroke recovery, restore hearing, and more. For example, functional near-infrared spectroscopy (fNIRS) is an imaging

technology that is currently used in research (e.g., on neurodevelopment, cognitive decline, psychiatric disease, rehabilitation, marketing, social interaction, and emotion perception) and can further be used as an input to brain–computer interfaces (BCIs) and be coupled with other inputs (e.g., physiological measurements) and technologies (e.g., electroencephalography [EEG], tDCS, BCI) to expand the range of questions and its applications.

In addition, companies such as Mindstrong Health are using machine learning methods coupled with data collected from human–computer interactions on smartphones to assess individuals' well-being and cognitive function. Studies indicate that measures of human–computer interaction (e.g., the latency between space and character or the interval between scroll and click) can serve as surrogates for cognitive traits and affective states (Dagum, 2018). As a result, such data could be used to detect symptoms or changes to mental health. This approach, known as digital phenotyping, holds promise for revolutionizing the field of psychiatry, yet it also raises ethical, legal, and social implications. Issues such as transparency, access, informed consent, privacy, and accountability must be addressed (Martinez-Martin et al., 2018).

How all of these technologies evolve over the coming decades—and the development of other enabling technologies—will further expand the capabilities of existing technologies and could lead to very different futures, depending on whether and how society chooses to govern and shape them and the simultaneous evolution of the broader geopolitical and social context.

Visioning

In the future, improved brain–machine interface technologies may enable broad access to "typing by brain" and direct brain-to-brain communication. Some even believe that in the future, human intelligence will be augmented with artificial intelligence via neural interfaces (Royal Society, 2019). In 2016, Elon Musk founded a company, Neuralink, focused on developing ultra-high bandwidth brain–machine interfaces to connect humans and computers. Musk has asserted that such technology could enable human "symbiosis with artificial intelligence" (Hamilton, 2020).

It is anticipated that going forward, there will be increasing convergence between "read" and modulation neurotechnologies, and with broader technologies such as artificial intelligence and robotics, radically expanding the kinds of questions asked, conditions treated, and applications developed. Emerging capacities to read, augment, network, and modulate brains have already and will continue to raise significant concerns about privacy, cognitive liberty, autonomy, coercion, justice, equity, and beyond, and will do so in ways that will undoubtedly reach across sectors as technologies and applications leave the lab and are put to use in the world.

In an effort to probe the kinds of worries the authors have about the trajectories of emerging technologies, to expand the range of lessons learned from each case, and ultimately to "pressure test" the governance framework, the authors have developed a brief "visioning" narrative that pushes the technology presented in the core case 10–15 years into the future, playing out one plausible (but imagined) trajectory. The narrative was developed iteratively in collaboration with a case-specific working group, with additional feedback from members of CESTI. All reviewers are acknowledged in the back matter of this paper. Each narrative is told from a particular perspective and is designed to highlight a small set of social shifts that shape and are shaped by the evolving technology.

Neurotechnology Case Visioning Narrative

Perspective: Chief human resources officer for a multinational software as a service (SaaS) company

Background

It is 2030, and BCIs have undergone several waves of innovation and investment over the last 10 years (2020–2030), resulting in small, powerful devices that are now readily available to patients and consumers. These devices allow for the acquisition, interpretation, and translation of brain signals into commands that can be transmitted to another individual or used to control an external device (e.g., computers, prosthetics, and other devices). Today, BCIs build on the early experience in the military, where prototypes were financed by DARPA and facilitated previously unfathomable image and data processing capabilities and focus among military personnel. This led to a rapid dissemination in the health care sector, as BCIs are now used in the treatment of a broad range of medical applications, including stroke rehabilitation, cerebral palsy, and treatment of depression, Alzheimer's disease, and ADHD. The applications outside of clinical care are as unimaginable today as the iPhone was in 1990: BCIs offer the promise of better health, better memory, better concentration, and a more collaborative world. They have been broadly adopted in Silicon Valley, especially among companies in the SaaS sector. The small size, modest cost, and user-friendliness of these devices, combined with provision of end-user control, led to widespread, though not uniform, acceptance. For example, devices could be turned on or off easily, and consumers were able to modulate and personalize the output (i.e., what types of brain signals can be transmitted). The fact that the military was an early adopter went a long way to alleviating fears about downstream risks for many employees. One company chose to offer BCIs to its workforce (full-time employees and contract workers), and within the first 18 months, 90 percent opted to use it.

Impact on Workplace and Office Culture

The company mailed BCI devices to the home addresses of consenting employees, which became an inflection point for transition to a 100 percent remote work environment. By enabling the remote sensing, recording, and transmission of brain signals

and thought patterns between employees, BCIs significantly enhanced group decision-making across our institution. Errors in interpretation, difficulties in interpersonal interactions, and judgement biases were all reduced due to a strengthening of communication feedback loops. Collaboration with colleagues at our international locations also improved because BCI enabled individuals to surmount language barriers. Our employees also reported improved focus, information retention, decision quality, and sleep as a result of sustained BCI use.

However, existing concerns around work–life integration were heightened. For example, how does one separate personal thoughts from professional thoughts? Ethical concerns have also been raised in light of recent provocative uses of BCI in Silicon Valley, specifically with respect to employee autonomy and patent infringement. There have been several reports of employers using EEG and artificial intelligence–mediated BCIs to monitor and reprogram the affective states of employees to "improve workplace culture" by making them more compliant, satisfied with working-conditions and compensation levels, and less likely to think of leaving the employer to pursue other opportunities.

What is the employee consent process, and what are the guardrails, regulatory and otherwise, to protect against harm (physical, emotional, and mental)? What form should corporate responsibility to employee stakeholders take in this context? Anticompetitive practices have also been described wherein BCIs were used to reverse engineer or "design around" a competitor's proprietary technology, such as noninvasive sensors.

Finally, the company completely revamped the data governance around company-owned BCIs after a foreign entity attempted to hack the chief financial officer's device and spread disinformation around the time of the investor call last quarter. The availability, security, and integrity of BCI-generated data are now included in the enterprise risk management and response program to prevent such threats in the future, whether they originate from state actors or economic competitors.

Employee Wellness and Health Care

The company's employee health office is now able to monitor the mental health and physiological states of employees. In collaboration with data scientists and neurocognitive researchers at Stanford University, brain wave and blood flow patterns transmitted to the office by employee BCIs combined with information about screen time, keystrokes, and response latency enabled the development of digital indicators for disease, often months in advance of clinical signs. When appropriate and indicated, their company was able to deliver a health intervention or "neuroceutical" intervention to its BCI remote monitoring platform.

Unfortunately, the company began to observe a worsening of certain mental health conditions in a subset of employees due to long-term and/or "off-label" BCI use (i.e., unapproved indications). For example, many employees reported negative health effects such as exhaustion, poor focus at work, and patterns of addictive behavior due to excessive BCI use for recreational purposes, for example, virtual reality video games, memory retention in poker tournaments, and online dating. The company also received isolated reports of people exhibiting dependence and experiencing withdrawal symptoms and psychological harm upon revocation of BCI access. Finally, the company discovered that off-label utilization patterns were as much interpersonal as they were intrapersonal. Shared use among family members became common, inviting unintended consequences on spousal and parental relationship dynamics. There were anecdotal reports of spouses or children using a family member's employer-issued BCI device to improve performance at work or school.

Many employees raised privacy concerns, indicating that they were afraid of losing their jobs or being given fewer desirable assignments if pre-existing mental illness could be detected and inadvertently broadcast to work supervisors during BCI use. Incidents like this also run the company afoul of provisions in California's Fair Employment and Housing Act, which prohibit discrimination of employees suffering from mental health issues. Furthermore, with the family unit occasionally now functioning as a "single user," unintentional access to and transmission of the personal data of nonemployees (i.e., affective states of family members and family relationship dynamics) presented novel privacy concerns. While unauthorized use by a family member was in violation of the terms and conditions associated with the BCI device, the company's ability to access privileged personal data of nonemployees was something that it had to account for and diligently protect against. To build trust and support the productivity of employees, the company made significant investments in its wellness programs, expanding its reasonable accommodation strategies for mental health concerns.

In recent years, there have been a growing number of sponsored legislations at the state and federal level to update labor laws to protect against workplace discrimination on the basis of BCI data similar to race, gender, and sexual orientation. Finally, we gave employees the ability to enforce a "right to erasure" with regard to personal BCI data at any time. This applied to 99 percent of employees at the company. A small group of senior executives are the exception to this rule: while they maintain the right to erase personal BCI data, thought patterns related to specific, high-value projects cannot be erased and are the property of the company. Furthermore, noncompete clauses prevent these executives from downloading this data and sharing it with competitors if they leave the company.

Concerns About Enhancement and Equity

Some employees have been tremendously excited about the potential to use company issued BCIs to enhance themselves. Applications are emerging that enable an individual to use a BCI to augment their own brainpower with superfast computing and artificial intelligence—as such, employees are now able to read and absorb vast amounts of information. Other employees are

downloading the information recorded by their BCI in the hopes of preserving their thoughts and memories in order to create digital avatars and achieve a form of "digital immortality." These behaviors have engendered a larger conversation about the disproportionate impacts of and access to BCIs across the workforce, that is, blue-collar versus white-collar and access of those from private companies versus the general public. For instance, several reports published in 2029 found that students from affluent backgrounds with access to BCI technology, relative to students without BCIs, exhibited superior academic performance: higher grades, lower dropout rates, and higher graduation rates.

A few media outlets have also written about the company's use of BCIs, citing the potential negative effects on equity, especially with regard to socioeconomic and pre-existing physical or mental impairment as defined by the Americans with Disabilities Act. Should the physical and cognitive augmentation opportunities made possible by BCIs be only available to the able-bodied or wealthy? Others have noted that individuals who do not work at companies subsidizing BCIs may not be able to access these devices, forcing them to rely on their own brainpower and unable to attempt digital immortality. The company's leadership has argued that they have a number of initiatives to improve community access to BCIs; furthermore, they feel that this is a problem that the government and not the private sector should solve. The FDA, OSHA, and FCC have yet to put forward an applicable regulatory framework for BCIs. These issues are compounded by the fact that the company's international footprint exposes the firm to very different jurisdictions around data privacy and protection in the markets where it is active.

Neurotechnology Case Study: Lessons Learned

Following are some of the lessons drawn from the preceding core case and visioning exercise that can inform the development of a cross-sectoral governance framework for emerging technologies focused on societal benefit.

- The coexistence of health and nonhealth applications can complicate governance.
- There is a need for a mechanism for awareness of and attention to what happens when a technology gets out in the wild (i.e., DIY).
- When considering potential federal regulators, think beyond the FDA (e.g., FCC, CPSC, OSHA).
- Professional societies of physicians, scientists, and ethicists working in this space can apply useful pressure as part of a governance ecosystem.
- There is flexibility and lack of oversight in the gray area that exists following the development of promising data regarding a new technology, but before proven efficacy and regulated products.
- Commercial drivers of R&D can play a prominent role in the evolution of a technology, even in the absence of robust data on efficacy.
- When minimal physical risks are posed by a technology, this can enable regulatory permissiveness.
- The historical context of a technology (e.g., the history of lobotomy, stigma associated with mental illness) may shape public perception and use.
- Opportunities for regulatory nimbleness have been revealed by the federal response to the COVID-19 pandemic.
- In the "age of surveillance capitalism," the collection and monetization of brain data is particularly concerning.
- Commercial availability of what are essentially medical devices raises concerns about privacy outside "covered entities."
- Attention needs to be paid to how risk scales; a governance ecosystem needs to be able to identify ways to monitor for specific combinations of people or populations, uses, and contexts that raise red flags, particularly for technologies with low physical risks.
- Use of new technologies in the workplace (whether voluntary or mandatory) may require particular attention.
- Governance needs to be dynamic in the face of new contexts and applications of a technology, that is, course-correct very quickly.
- Poor access to safe, effective emerging technologies can widen existing inequalities, for instance, related to race, socioeconomic status, and disability.

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