Responsible innovation in neurotechnology, practical examples from translational projects

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Progress in neurotechnology is advancing rapidly driven by unmet needs for therapies to treat neurological disorders. New technologies raise ethical questions and responsible innovation is needed at every step of the development process.
Here we describe two research projects breaking new ground in neurotechnology and neurobiology respectively. The first, a brain-computer interface, enables people who are completely locked-in to communicate in real time using their brain signals to control a communication device. The second assesses the feasibility of using photobiomodulation (PBM) as a therapy in the fight against neurodegenerative disorders like Parkinson's and Alzheimer's disease.
We briefly consider the ethical aspects of both projects and conclude that organizations developing new neurotechnologies should consult with experts in neuroethics and put quality systems which require development in line with accepted international standards in place early in the development process. They should additionally engage in an open dialogue with society around the impact of their technology. Finally, they should anticipate potential unintended use of new technologies and engage with professional organizations to facilitate the translation of applied research ethics into government policy.

Innovative technology and the need for ethics

Research and development in neurotechnology is advancing rapidly, presenting new frontiers for researchers, clinicians, patients, and the public alike. Progress is driven by unmet needs for therapies to treat neurological disorders ranging from paralysis to neurodegenerative disease. Globally, stroke is the second biggest cause of death and the third leading cause of disability worldwide [1,2] while neurological disorders like Alzheimer's disease are on the rise with more than 50 million people currently living with some form of dementia [3].

The potential for neurotechnology to offer solutions to these growing global challenges is driving a new generation of researchers and companies to innovate. They are exploring technology-aided stroke rehabilitation, trialing brain-controlled communication for people with locked-in syndrome and conducting clinical trials with technologies like deep brain stimulation (DBS) for the treatment of Alzheimer's disease [4]. Neurotechnology has already seen success. Spinal cord stimulation has been shown to be clinically effective at restoring sensory-motor functions in patients with spinal-cord injury [5]. Brain-computer interfaces (BCIs) have been used to restore communication in people with neurological impairments and loss of muscle control [6]. And DBS has been used to treat symptoms associated with Parkinson's disease and essential tremor [7].

There is also new technology emerging for healthcare applications in the fields of molecular and cellular biology. Novel techniques such as CRISPR have led to the promise of precise gene editing for drug discovery [8] and several diseases [9] and stem cell therapies have the potential to

(1) https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death
(2) https://www.world-stroke.org/publications-and-resources/resources/global-stroke-fact-sheet
(3) https://www.who.int/health-topics/dementia#tab=tab_1

(4) https://www.frontiersin.org/articles/10.3389/fnagi.2021.619543/full
(5) https://www.nature.com/articles/s41586-018-0649-2
(6) https://www.nejm.org/doi/full/10.1056/nejmoa1608085
(7) https://pubmed.ncbi.nlm.nih.gov/15097290/
(8) https://www.nature.com/articles/d41586-018-02477-1
(9) https://www.nature.com/articles/d41586-021-01776-4

address a range of disorders such as spinal cord injury [10,11] and stroke [12,13] but a number of questions remain as to their ultimate safety and efficacy. Since the debut of CRISPR-based gene editing, the prospect and relative ease of genetic modification of whole organisms has become a reality. However, the long-term consequences of allowing deliberate mutations to pass from one generation to another and the impact on the wider population must be carefully considered and discussed among society and lawmakers.

While the scale of human benefit from these advances is potentially huge, every new discovery or emerging technology must be assessed for not only the scientific and technical feasibility, but also the ethical, legal and social implications to ensure that the progress made is ethically balanced and considers the benefits and potential risks from both an individual and a societal perspective.

For organizations developing new technologies destined for human clinical applications, this means implementation of regulatory and quality processes from an early stage. Development of new medical technologies is strictly regulated. Any innovation that is to succeed on the journey from research to clinic must adhere to the safety and ethics requirements of medical regulations at every step of the way.

The quality of raw materials, components, and subsystems to be included in a device or used in a clinical trial is controlled and documented. The trials themselves are carefully designed to optimize the assessment of efficacy and safety [14] and include plans to mitigate any potential risks. Proposals are reviewed and approved by ethics committees and regulatory authorities before trials begin.

To ethically justify a research project involving human participants, the researchers must demonstrate high scientific quality and integrity in which the risk: benefit ratios to participants are acceptable and in which the protection of the individual takes precedence over the scientific interests of society [15].

While existing regulation protects society from known risks, legal frameworks must evolve to keep pace with rapid rates of technology development.

A 2019 government survey [16] in the UK found that three quarters of the public questioned believed that the government should delay new technologies until scientists are certain of their safety. Around a third of people were concerned that the speed of development limits the extent to which government can properly exert control. The findings suggest that in addition to the existing legal frameworks, organizations that develop emerging technologies, have a responsibility to confront ethical questions as new technologies emerge.

(10) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2678281/
(11) https://journals.sagepub.com/doi/full/10.1177/0963689721989266
(12) https://www.elsevier.es/en-revista-medicina-universitaria-304-articulo-current-state-perspectives-stem-cell-S1665579616300710
(13) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5066440/
(14) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6434767/
(15) https://swissethics.ch/en/
(16) https://www.kantar.com/uk-public-attitudes-to-science

Working with professional organizations and advisory bodies, including experts in neuro and bioethics, helps drive development of new engineering standards and good practice guidelines; and helps to ensure that policy evolves at the same rate as technology [17].

Engaging society in conversations regarding the best future for emerging technologies while ensuring that information is readily available and comprehensible for all, ultimately builds trust in science and technology organizations and builds scientific capacity in the population.

A brain-computer interface to enable people who are completely locked-in to communicate

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder in which deterioration of the nervous system responsible for voluntary movement eventually leads to paralysis, but in which the cognitive parts of the brain often continue to function normally. ALS is also known as Lou Gehrig’s disease and motor neuron disease (MND).

Some people with ALS progress into a complete locked-in state (CLIS) in which they lose the use of all muscles and survive with artificial ventilation and feeding. In CLIS, people have no way to communicate.

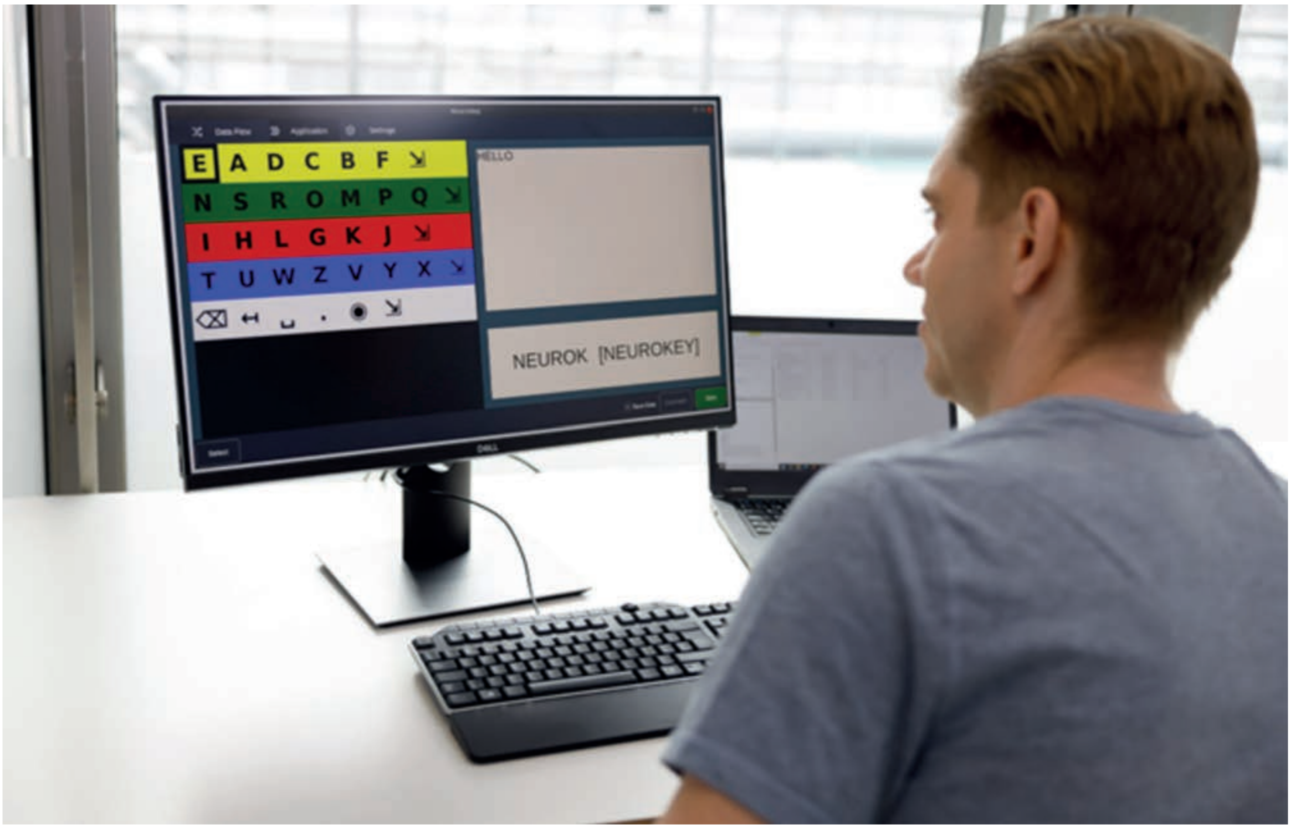
When people can no longer speak, but still have some remaining movement ability, they often use assistive communication devices to express themselves through a computer. Such devices include eye trackers, switches that detect muscle activity, and sip and puff devices that measure air pressure in inhaled or exhaled breath.

There is evidence that people with ALS can have a high sense of well-being, even in a locked-in state [18], and so the ability to communicate is important to ensure continued high quality of life and appropriate care.

As part of a single patient case study, researchers are working with a participant with ALS, his family and the departments of neurology and neurosurgery at a hospital in Germany. The goal of the project is to determine whether people with advanced ALS, who can no longer use assistive devices to communicate, can voluntarily form words and sentences with the help of an implanted BCI system.

Two microelectrode arrays inserted into the surface of the motor cortex – the part of the brain responsible for movement – detect neural signals. A wired connection sends the neural data to a computer for processing. Custom software (NeuroKey) decodes the data and runs an auditory feedback speller that prompts the user to select letters to form words and sentences. The user learns how to alter their own brain activity according to the audio feedback they receive.

(17) https://standards.ieee.org/industry-connections/neurotechnologies-for-brain-machine-interfacing.html
(18) https://n.neurology.org/content/93/10/e938



The NeuroKey communications platform enables people who are completely locked-in to communicate in real time. The software decodes neural data and runs an auditory feedback speller that prompts the user to select letters to form words and sentences (credit: Wyss Center).

NeuroKey software for communication is a CE-marked medical-grade platform optimized for high channel count, high frequency data processing in real time. It allows the team to rapidly change how the data is processed through a modular programming interface. Future applications include the integration of other assistive devices, including home automation systems and emergency alarms.

The results of the project guide the development of future devices including fully implantable brain-computer interfaces for the restoration of communication and movement. The aim is to bring the latest assistive technology closer to safe, long-term daily use at home. Such tools are key for the CLIS ALS population, but also have potential to help people affected by other diseases that impact their ability to move or communicate including stroke, spinal cord injury, late-stage muscular sclerosis, late-stage Parkinson's disease and severe cerebral palsy.

From an ethical perspective, the use of BCIs raises important questions about data privacy and ownership, long-term use and maintenance of the technology, and about decision making in the context of use. As brain data decoding improves, researchers and participants must consider the potential for brain data to reveal more in the future than it does today. For example, data recorded with a BCI could, in the future, reveal sleep habits, medications or participant-typed text. Another important consideration is who decides when devices should be switched on: should it be the participant themselves, the caregivers or the researchers? If a device is working as an emergency alarm, would it be ethically unacceptable for that device to ever be switched off? If so, who is responsible for ensuring continuous system maintenance and security?

Learning from established medical ethics can help navigate this newly emerging ethical landscape, but these are questions that must be carefully considered through interdisciplinary collaborations with scientists, engineers, and ethicists while developing BCI technology.

Shining a light on neurodegenerative disorders – Photobiomodulation

From photosynthesis in plants to the photosensitive cells in our eyes, the ability of light to induce a biochemical reaction in living cells has long been known. Using near infra-red light, researchers have explored the potential of this phenomenon, known as photobiomodulation (PBM), to stimulate healing, relieve pain and – in recent years – as a therapy for brain disorders [19].

Promising animal trial data, from several independent laboratories [20,21,22], have suggested that illuminating the brain may slow down neurodegeneration and have protective effects, while a trial [23] in France, is exploring

(19) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6664299/
(20) https://pubmed.ncbi.nlm.nih.gov/26456231/
(21) https://pubmed.ncbi.nlm.nih.gov/24994540/
(22) https://pubmed.ncbi.nlm.nih.gov/30625333/
(23) https://clinicaltrials.gov/ct2/show/NCT04261569

the effects of PBM deep inside the brain in people with Parkinson's disease.

A hallmark of neurodegenerative disorders is the accumulation of misfolded, self-replicating proteins in the affected brain regions. These rogue proteins cluster in toxic aggregations, that damage mitochondria – the powerhouses of cells – and cause other harmful events that ultimately kill neurons.

As the proteins multiply, and propagate from one cell to another, the disease spreads across the brain.

While there are likely to be several mechanisms at play, enhancing mitochondria with PBM appears to trigger a cascade of biochemical reactions which counteracts the damaging effects of the rogue proteins. There is also increasing evidence to suggest that PBM may also prompt neuroprotective mechanisms that reduce the harmful impact of the proteins on the other parts of the cell.

The encouraging results from studies so far, and parallels in protein pathology between Parkinson's disease and other neurodegenerative disorders, suggest that PBM may also work as a therapy for dementia.

To investigate this hypothesis, researchers are exploring the biological mechanisms behind the effects of PBM in Parkinson's disease, Alzheimer's disease and frontotemporal dementia. Using multiple preclinical models that mimic the key features of the diseases, researchers are assessing the therapeutic potential of PBM alone as well as in combination with existing therapeutic drugs and state-of-the-art therapies such as electrical deep brain stimulation.

The possibility of light stopping the spread of rogue proteins to slow the progression of neurodegenerative disease in the brain has yet to be definitively demonstrated. However, if such therapies are shown to be successful, their use beyond disease treatment must also be verified. If mitochondrial enhancement could be used to boost neuronal functioning, PBM could fall into the category of therapies that improve cognition in healthy individuals, presenting challenges in terms of regulation. The use of neurotechnologies for enhancement in education, the workplace, the military and in wider society poses numerous questions [24] including how to manage regulation across societies and global populations. There is precedent for controlled use of cognition enhancing substances [25] but, as new technologies emerge for treating disorders like dementia, the opportunities for unintended use must be carefully considered.

Conclusion and priorities

The research examples described here are at different stages of clinical translation and present very different ethical considerations. While the use of BCIs for communication raises questions about data privacy and security, equal access and responsibility for patients using the technology in the long term; the development of PBM as a therapy presents questions about how the unintended use of new technologies should be considered along-side their therapeutic use.

In both examples there are close similarities in the priorities necessary to ensure responsible innovation in neurotechnology. A study assessing the ethical dimensions of brain-controlled prosthetics found accountability, responsibility, privacy, and security to be key [26]. These four guiding principles form a good basis for neurotechnology research that can realize the potential to improve countless lives while ensuring solid ethics. Ongoing global efforts such as the IEEE Neuroethics Framework [27] and the OECD's responsible innovation in neurotechnology international standard [28] will be key to providing guidance to scientists, engineers and companies developing novel technology, and to government policy makers who must consider the impact of technology on society and develop appropriate policies to safeguard the populace. In a knowledge-based, open society in which public opinion influences political decision making, every citizen should have the tools they need to make an informed choice. Research organizations and companies that are pushing the boundaries of neurotechnology have a responsibility to contribute to the societal knowledge base, to engage with professional organizations on the development of new standards and best practices, and to help facilitate the shift from applied research ethics to legal frameworks and regulation.

While the highly regulated field of medical device development requires strict adherence to national and international standards, a culture of research excellence, regulatory compliance and quality control embedded in organizations at both the individual level and at a project level is the crucial first step towards ensuring that research is always safe, is of the highest quality and is of impeccable moral integrity.

(24) https://www.cell.com/neuron/fulltext/S0896-6273(17)31140-6?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0896627317311406%3Fshowall%3Dtrue
(25) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2690227/

(26) https://science.sciencemag.org/content/356/6345/1338.abstract
(27) http://brain.ieee.org/wp-content/uploads/sites/52/2020/03/ieee_brain_neuroethics_framework_double-sided-031920.pdf
(28) https://www.oecd.org/science/recommendation-on-responsible-innovation-in-neurotechnology.htm