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Reengineering neurotechnology: placing patients first

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Neurotechnologies that measure and modulate brain activity have not yet reached widespread clinical relevance. To accelerate translation into patient care, we propose three strategic adjustments in neurotechnology research — to consider the scope, scalability and stakeholders.

Neurotechnologies that measure and modulate brain activity hold great promise to improve the diagnosis and treatment of brain disorders[1]. Six out of the ten leading causes of disability worldwide are amenable to neurotechnological approaches[2] such as direct invasive and/or non-invasive modulations of brain activity, or indirect modulations of brain activity by stimulating peripheral nerves (Fig. 1). Depressive and anxiety disorders, pain states and hearing loss top this non-exhaustive list. Other disorders with sensory, cognitive and affective symptoms such as substance-use disorders, stroke, autism and dementias including Alzheimer's disease are further examples of neurotechnology targets that are worth pursuing.

Remarkable progress has recently been made in selected patient groups. For instance, brain–computer interfaces are increasingly effective in replacing and/or restoring motor and speech function in patients with limb amputations, spinal cord injury or brain injury[3,4]. However, these approaches are only appropriate for comparatively small numbers of patients. Thus, contrary to public perception, neurotechnologies have not yet reached a stage of widespread clinical relevance. To identify means to accelerate the translation into patient care, we have assembled an interdisciplinary group of experts that cover the fields of neuroscience, neurology, neurosurgery and psychiatry, ethics and social sciences, engineering and computer science. We propose three strategic adjustments in neurotechnology research and development that are designed to overcome current limitations in the domains of scope, scalability and stakeholders ('3S principles'; Fig. 2). The proposed 3S principles are intended as guidelines for researchers and those who fund and guide neurotechnology research to eventually accelerate the translation of neurotechnology into patient care.

Fig. 1 | Leading causes of disability worldwide. The chart shows the 10 leading level 3 causes of disability assessed by the years lived with disability (YLDs) summary measure in the 2019 Global Burden of Disease (GBD) study[2]. Blue segments indicate the contribution of diseases with prominent sensory, cognitive and/or affective symptoms. Together, these disorders cause 69% of YLDs of the 10 leading causes. The outer circle indicates disorders whose symptoms can potentially be targeted by neurotechnologies that measure and/or modulate brain activity. Data were compiled using the GBD Results Tool.

Scope

First, we propose broadening the scope of neurotechnology applications to neuropsychiatric symptoms and disorders of mental health. Traditionally, neurotechnologies focus on restoring motor functions — for example, in spinal cord injury or in Parkinson's disease. However, cognitive, affective and sensory symptoms are extremely widespread and impose an enormous burden on patients, healthcare systems and societies (Fig. 1). For example, depression and chronic pain are among the most important causes of lasting disability worldwide[2]. The treatment of these disorders is often unsatisfactory, and new drug approvals have been scant in recent years[5]. There is therefore an urgent need for new non-pharmaceutical treatment strategies. This particularly affects highly prevalent diseases such as depression and anxiety disorders and chronic pain.

We further argue that integrating neurotechnologies with established treatment approaches is particularly promising. Thus, we should reconsider neurotechnologies not only as alternatives, but as complements to current treatments. Recent studies have shown how the combination of brain stimulation with psychotherapy and/or drug treatments can act synergistically[6].

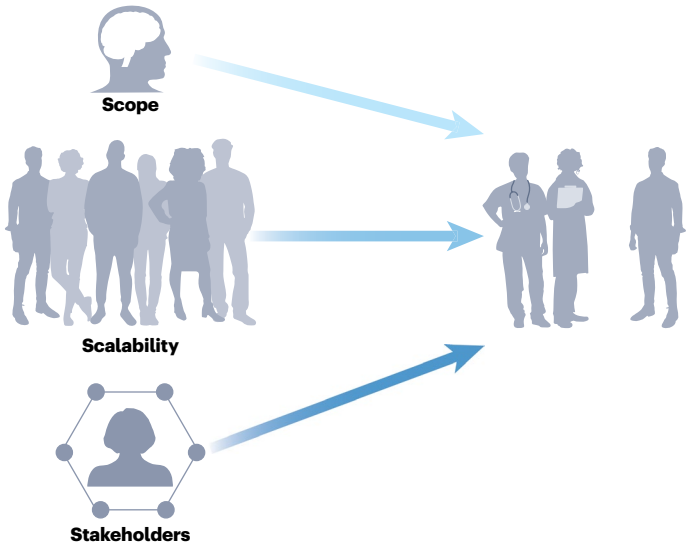

Fig. 2 | 3S principles. Strategic adjustments in the domains of scope (targeted brain systems and symptoms; for example, motor, sensory, cognitive and affective), scalability (applicability to large numbers of patients) and stakeholders (needs of patients, caregivers and societies) are proposed to accelerate the translation of neurotechnologies into patient care.

Moreover, we should view neurotechnologies not only as new treatment approaches but also consider their potential for the classification, diagnosis and prognosis of mental diseases and to predict treatment responses. For example, specific brain activity patterns, detected by state-of-the-art artificial intelligence (AI)-based methods, can predict responses to drug or brain-stimulation treatments in depression[7]. In clinical practice, it is notoriously difficult to predict how an individual patient may respond to a certain treatment. Thus, such biomarkers that are based on measurements of brain activity would be tremendously helpful to tailor the individualized treatment of disorders of mental health.

Finally, we propose that the unspecific effects of neurotechnologies should be carefully considered. The efficacy of any medical procedure depends on the specific effects of the treatment itself, and also on unspecific effects such as the clinician's and patient's expectations[8]. Such unspecific effects can induce positive (placebo) as well as negative (nocebo) effects. Owing to their novel character, the aura surrounding them and possible associations emerging from popular discourse, neurotechnologies are likely to induce strong expectations, to which neurological and psychiatric symptoms are particularly sensitive[9]. The development of neurotechnologies should therefore carefully consider unspecific treatment effects. For research purposes, unspecific effects should be minimized. By contrast, for maximum clinical efficacy, unspecific placebo effects should be maximized[8].

We suggest that by following the outlined approach of broadening the scope of neurotechnologies, methods to record and modulate brain activity can be seamlessly integrated with pharmacological and behavioral approaches for the diagnosis and treatment of mental health disorders. Such multimodal approaches would also properly account for the complexity of bio-psycho-social disease models of neuropsychiatric disorders[10].

Scalability

Second, we propose emphasizing the scalability of neurotechnologies to large numbers of patients. So far, research exploring cutting-edge neurotechnologies considers scalability relatively late in the typically proof-of-concept-based innovation process. Considering scalability during the early steps of research and development could guide activities towards approaches that are the most promising for translation into clinical treatments for large numbers of patients. This applies equally to invasive and non-invasive neurotechnologies that measure and modulate neural activity from inside and outside the skull, respectively.

Invasive neurotechnologies have an unparalleled precision and efficacy and can thus perfectly serve the diagnosis and treatment of brain disorders. In addition, they can provide invaluable insights into the mechanisms of brain disorders, which are indispensable for designing invasive and non-invasive neurotechnological interventions. However, their invasiveness entails risks, efforts and costs that causes reservations among patients and clinicians and eventually hampers scaling to large numbers of patients. To facilitate scalability, the benefit-to-risk ratio of invasive neurotechnologies should be assessed and optimized at the earliest stages in project design and implementation. For example, maximizing benefits can be achieved by increasing the number of channels on recording electrodes, tightening the tissue–electrode coupling, extending the coverage of brain areas and advancing analysis and stimulation algorithms[11]. Moreover, benefits critically depend on the long-term stability of devices, which should also be considered early in the development process. Minimizing harm can be achieved by designing electrodes with smaller footprints and reduced invasiveness to mitigate the brain's foreign body response.

Non-invasive neurotechnologies that measure and modulate neural activity from outside of the head can be particularly well scaled up to large patient numbers. For example, electroencephalography (EEG) recordings of brain activity are increasingly versatile. Novel EEG electrodes and smaller devices now allow for mobile use, and new AI algorithms can assess the complex brain dynamics that underlie mental disorders with unprecedented precision[12]. Similarly, non-invasive stimulations of brain activity have been substantially refined in recent years[13]. Methods such as transcranial direct current stimulation, transcranial alternating current stimulation and transcranial magnetic stimulation are increasingly precise and effective[14]. Further technological refinements promise to modulate brain activity even in deep brain structures. Moreover, closed-loop approaches that modulate brain activity on the basis of the momentary brain state might enable particularly effective, individualized neuromodulation[15]. Considering these developments, we suggest prioritizing the development of non-invasive neurotechnologies that are particularly well suited for scaling up to large numbers of patients.

Stakeholders

Third, we propose engaging with patients, caregivers and healthcare providers more actively, and including them in the innovation process early on. The development of neurotechnologies is often shaped by the researchers' technical expertise and interests rather than by the needs of patients and societies. Involving patients at all stages of research and development can help to focus on approaches that serve the most pressing needs of patients and are of most use to them. Such a stakeholder involvement is in line with policies of major international funding institutions. Ethicists and social scientists should guide and mediate this involvement. We specifically propose to draw on responsible research and innovation (RRI) and embedded ethics and social science

approaches to facilitate co-creation processes in socially responsible and inclusive ways[16]. Such an integrative approach promises to broaden the focus from the technical feasibility of neurotechnologies to patients' needs, social inclusiveness and ethical responsibility.

Challenges

Neurotechnologies promise to advance the diagnosis and treatment of neuropsychiatric disorders. However, to translate neurotechnologies into patient care, major challenges must be met. First, the effects of neuromodulatory approaches on brain activity and behavior are highly variable. This is in part due to inter-individual variability in the structure and function of the brain, as well as to intra-individual fluctuations of brain activity. Individualized approaches that take into account these inter-individual variations or even closed-loop approaches that consider intra-individual variations in momentary brain state might help to meet this challenge. Second, the proposed strategic adjustments primarily address researchers and those who guide and publicly fund neurotechnology research. These adjustments must be brought in line with the interests of industry, which are primarily driven by market laws and entail the risk of overplaying the promises of neurotechnologies. Third, implementing neurotechnologies in lower- and middle-income countries is particularly challenging. Thus, it is essential that in considering scalability, the economic and technical feasibility in lower- and middle-income country settings is carefully scrutinized during all stages of the development process.

Conclusions

We propose that the 3S principles we have outlined here – that is, considering the scope, scalability and stakeholders of neurotechnologies applied to brain disorders – can serve as guidelines for researchers and those who fund research to accelerate the translation of neurotechnology into patient care. The 3S principles mandate a new culture of neurotechnology research and development in which engineers work together with clinicians, neuroscientists, data scientists, ethicists and social scientists to co-create neurotechnological solutions for the most urgent healthcare challenges, with patients' and caregivers' needs at the center of all efforts. By adopting such a broadened, interdisciplinary, co-creative and patient-centered approach, we anticipate that neurotechnology will be able to live up to the promise of improving the lives of many, not just a select few.

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