NUFFIELD COUNCIL ON BIOETHICS

Literature Review: Neurotechnology

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Executive Summary

This literature review was commissioned by the Nuffield Council on Bioethics to outline the key developments, applications, and impacts of neurotechnologies in active use between 2013 to 2024. This includes the ethical, social, policy, and legal implications of these developments.

As an output under the Nuffield Council on Bioethics' 'Mind and Brain' priority area, this review seeks to scope the current landscape and ethical implications of neurotechnology research and policy. It outlines the existing state of specific neurotechnologies and associated key themes across research and clinical practice.

Neurotechnology use for therapeutic purposes has extended to a range of neurophysiological and neuropsychiatric conditions, but there have been calls for more evidence, standardised study protocols, and robust clinical trial designs prior to making these technologies available. Another area of focus is on device obsolescence and the specific ethical implications of this phenomenon. Regulatory, social, policy, and legal developments – such as Brexit and the Covid-19 pandemic – have had a significant impact on medical device regulation and neurotechnology access in the UK.

This review outlines recurring themes from primary and secondary literature searches to address questions about device safety, equitable access to neurotechnology and research participation, continued access to neural devices, and other neuroethics considerations. As neurotechnologies become increasingly accessible – both in healthcare and through direct-to-consumer approaches, there is a need for proactive consideration of ensuring device safety, treatment personalisation, and promoting innovation in ethically robust ways.

Introduction

The Nuffield Council on Bioethics (NCOB) 2013 report, *'Novel neurotechnologies: intervening in the brain*,'[1] developed an ethical framework to guide the development, regulation, and promotion of neurotechnologies. It outlined four groups of neurotechnologies, namely transcranial stimulation (including electric and magnetic stimulation), deep brain stimulation (DBS), brain-computer interfaces (BCIs), and neural stem cell therapies (NSCs). A range of other neurotechnologies has been in active use between 2013 to 2024, which are included in this report. The neurotechnologies outlined in the NCOB's 2013 report have also had further developments and applications since the report's publication, which are included in this review.

A range of taxonomies can be used to distinguish between types of neurotechnologies. For example, Ligthart et al.'s (2023) classification system defines three types of neurotechnologies, which can be divided by level of invasiveness. These include neurotechnologies for: "(1) measuring brain structure or function, (2) intervening in brain structure or function, (3) measuring and intervening in brain structure or function."[2] Cinel et al.'s (2019) classification includes neurotechnologies "observing and influencing brain activity based on temporal resolution, spatial resolution, invasiveness […], and portability".[3] The Regulatory Horizons Council's (RHC) proposed neurotechnology taxonomy in the United Kingdom divides neurotechnological devices based on their level of invasiveness, followed by their function (i.e. recording or modulation).[4]

As this review focuses on groups of neurotechnologies, the RHC's taxonomy is difficult to replicate given that their definition of neurotechnologies focuses on *devices*. However, to best align this review with the recently accepted practice for medical device regulation, separate sections will cover non-invasive and invasive neurotechnologies that are most commonly categorised in either category. Neuroimaging technologies and BCIs will be excluded from these categories as, depending on the device or combination of systems used, they may be either invasive or non-invasive. Instead, these categories and NSCs will be summarised in separate sub-sections.

Section 1 summarises neurotechnologies that have been in active use between 2013 to 2024. These include neuroimaging technologies, neuromodulation technologies, and NSCs. References are made to findings on specific conditions that have been studied or used for treating neurophysiological and neuropsychiatric conditions.

Section 2 defines and explores device obsolescence alongside associated concerns. It draws from a 2024 proposed definition on the matter, alongside previous patients' and research participants' experiences with device obsolescence, including involuntary device explantation and associated ethical implications.

Section 3 outlines the legal, regulatory, and policy landscape of neurotechnology in the United Kingdom (UK) in light of Brexit, neurotechnology advances, and the Covid-19 pandemic.

Sections 4 and 5 capture recurring themes from this review's primary search sources on robust and diverse clinical trials and neurorights, including implications over neurotechnology impact on personhood and considerations on post-trial access.

The methodology and research approach undertaken to produce this report is covered in the Appendix, which outlines the review's research questions, primary keyword searches, and the inclusion and exclusion criteria.

1: Active Neurotechnologies

This section outlines types of neurotechnologies that have been in active use between 2013 to 2024. It outlines developments in neuroimaging technologies, neuromodulation technologies, brain-computer interfaces (BCIs), and neural stem cells.

Neurotechnologies can use either open-loop or closed-loop feedback, which is applicable for both invasive and non-invasive neurotechnologies. Open-loop systems apply pre-programmed stimulation to targeted areas, whereas closed-loop systems modulate based on continuous monitoring and decoding of brain or neural activity.[5]

Key points:

- A range of invasive and non-invasive neurotechnologies have been in active use between 2013 to 2024. These include neuroimaging technologies, neuromodulation technologies, BCIs, and neural stem cells.
- Neuroimaging technologies can be invasive or non-invasive. They can be used on their own or in conjunction with other types of neurotechnologies, such as NIBS, BCIs, invasive technologies, or other neuroimaging devices.
- Non-invasive neuromodulation technologies can perform their functions through electrical stimulation, magnetic stimulation, or low-intensity ultrasound. The most commonly used technologies are electroconvulsive therapy, transcranial electric stimulation, and transcranial magnetic stimulation.
- Key types of invasive neuromodulation technologies include deep brain stimulation, vagus nerve stimulation, spinal cord stimulation, dorsal root ganglion stimulation, and responsive neurostimulation.
- Brain-computer interfaces are systems that translate commands sent through brain signals into an action, which can contribute to restoring or mitigating a range of emotional-cognitive, motor, and sensory functions. BCIs are often combined with neuroimaging technologies and other neuromodulation technologies to optimise patient benefit for specific conditions. Many BCIs are also combined with advanced artificial intelligence (AI) algorithms to perform their functions.
- Neural stem cells have been studied for the potential treatment of a range of neurological conditions due to their high regenerative potential, ability to self-renew, and ability to differentiate into different types of cells to provide neurohabilitative benefits.

1.1. Neuroimaging Technologies

Neuroimaging (or ‘neurorecording’) devices are used to record brain signals to collect, measure, analyse, or process data.[4]

Non-invasive neuroimaging technologies record this information from the surface of the body. They include:

1. extracranial electroencephalography (EEG),
2. magnetoencephalography (MEG),
3. magnetic resonance imaging (MRI),
4. functional magnetic resonance imaging (fMRI),
5. near-infrared spectroscopy (NIRS)
6. functional near-infrared spectroscopy (fNIRS).[2,4]

Invasive neuroimaging technologies are implanted inside the body to record brain data. These include intracranial EEG (ECoG) – whereby electrodes are placed on the brain's surface to record activity on the cerebral cortex – and stereo-electroencephalography (sEEG), whereby electrodes are implanted in specific brain regions.[2]

Neuroimaging technologies can be used on their own or in conjunction with other types of neurotechnologies, such as NIBS, BCIs, invasive technologies, or other neuroimaging devices.[4]

1.2. Non-Invasive Brain Stimulation (NIBS) Technologies

There are several non-invasive brain stimulation (NIBS) technologies currently used to treat or manage a variety of neurophysiological, neuropsychiatric, and neurological conditions. These include convulsive technologies, neuroimaging technologies, and technologies that stimulate the brain and/or the nerves from the surface. These technologies are considered non-invasive because they do not require surgery or implantations, as opposed to invasive neurotechnologies.

This section defines, and outlines the use of, neurotechnologies that perform neuromodulation through electrical stimulation, magnetic stimulation, or low-intensity ultrasound.

Electrical Neurostimulation

Electroconvulsive therapy (ECT)

Convulsive technologies have been used for patients with treatment-resistant conditions, such as major depression and bipolar disorder. Electroconvulsive therapy (ECT) is a convulsive therapy which induces a generalised seizure to create therapeutic effects. In ECT, this is done through sending an electrical current through the body by placing electrodes on the patient.[6] Comparative trials and meta-analyses of ECT to date have predominantly focused on major depression. The risks of ECT are relatively low and it is considered an effective procedure for treatment-resistant depression. It can also benefit patients with bipolar disorder, schizophrenia, schizoaffective disorder, catatonia, and neuroleptic malignant syndrome.[7] Although ECT generally presents an appropriate safety

profile, there are increased anaesthesia-associated risks for patients with comorbid conditions.[8]

Transcranial electric stimulation (TES)

In TES, electrodes are attached to the patient's scalp and an electrical current is applied to stimulate the brain. Transcranial alternating current stimulation (tACS) and transcranial direct current stimulation (tDCS) are modes of TES, which differ by the frequency of electric currents. tACS involves direct delivery of alternating currents to modulate excitability in the cortex, whereas tDCS generates a low-intensity, continuous current between at least two electrodes.[9–11]

tACS is more precise than tDCS and has been optimized through alternative combined techniques, such as high-definition tACS, phase-shifting tACS, amplitude-modulated tACS, temporal interference (TI) techniques, and intersecting short pulses (ISPs).[12] Particularly, TI exhibits high temporal and spatial precision present in invasive brain stimulation technologies while remaining a non-invasive option for brain stimulation.[13] However, despite this potential, TI usage to date has been limited to pre-clinical studies.

Another TES with a low-intensity alternating current is transcranial random noise stimulation (tRNS), which has lower discomfort levels than other TES NIBS technologies.[12,14]

TES has been studied for a range of conditions and has shown significant potential. For example, tDCS effectiveness has been considered significant in Singapore, where it is an approved treatment for fibromyalgia.[15] tACS and tRNS have also shown promising results in improving fibromyalgia symptoms.[11] However, the number of studies for other specific conditions has often been too limited to draw conclusive evidence on effectiveness. For example, although treating anxiety disorder using NIBS has mainly been explored through tDCS usage,[15] its effectiveness to date has been unclear.[9] tDCS has also been proposed as a clinical application for cerebral palsy. However, whereas some systematic reviews indicate effectiveness, others cite substantial limitations in establishing the extent of likely effectiveness.[15] Consideration has also been given to using tDCS as a treatment for patients with autism spectrum disorder, but reliable clinical efficacy cannot be asserted at this stage due to a need for more large, randomised, sham-controlled trials with robust experimental designs.[15]

Although there are fewer studies, the effectiveness of TES has also been tested in treating other neurological and psychiatric conditions, such as substance abuse, choreas, aphasia, and attention deficit hyperactivity disorder (ADHD), among others.[10,15,16] Interestingly, TES has also been used to examine condition progression rather than treatment, such as tACS for Alzheimer's disease (AD).[10]

Reduced impedance non-invasive cortical electrostimulation (RINCE)

RINCE is an electrical stimulation NIBS technique, not often used in clinical practice, whereby electrodes are placed on the patient's scalp to allow electrical currents to reach deeper into the patient's brain cortex.[17] Despite limited studies and research using RINCE, it has been cited as a treatment avenue with statistical and clinical significance for fibromyalgia.[12]

Non-invasive vagus nerve stimulation (nVNS)

nVNS is an alternative, non-invasive neuromodulation technique to vagus nerve stimulation (VNS) (discussed below). It stimulates the vagus nerve to provide therapeutic effects. In nVNS, neurostimulation devices activate either the cervical vagus nerve or the auricular branch of the vagus nerve through electrical stimulation.[18] nVNS has been investigated as a potential treatment for tinnitus, pain, cerebral stroke management, epilepsy, and migraines.[19,20] Several nVNS devices are available in Europe for the treatment of epilepsy, pain, and depression.[21] In December 2019, the UK National Institute for Health and Care Excellence (NICE) supported the use of an nVNS device to treat cluster headache within the NHS, allowing continued treatment for patients who exhibit symptom relief within the first three months of usage.[22]

Cranial electrotherapy stimulation (CES)

In CES, electrodes are placed on the patient's head to send a low-intensity electrical current, currently used to treat anxiety disorders, depression, and insomnia.[23] It differs from ECT and tDCS based on the placement of electrodes, the waveform used, and the intensity of the electrical current.[24] Several CE devices have been approved in the European market and sponsored studies have taken place following this approval, such as the Alpha-Stim AID CES medical device for generalised anxiety in the UK.[25]

Transcutaneous electrical nerve stimulation (TENS)

TENS is a NIBS technique where electrodes are placed on the patient's skin to send electrical stimulation through a small, battery-operated device to provide short-term pain relief.[26] TENS devices can be accessed as direct-to-consumer (DTC) technologies, including in the UK. TENS has been noted to have clinical benefits for treating pain in a range of conditions, but there are persisting disputes as to its clinical reliability and efficacy.[27]

Magnetic Neurostimulation

Transcranial magnetic stimulation (TMS)

As opposed to TES, TMS uses inductive electromagnetic stimulation instead of electrodes to induce stimulation.[28] TMS is widely used for diagnostic, prognostic, and therapeutic purposes for a variety of conditions, often as repetitive TMS (rTMS) to provide

long-lasting effects.[29,30] TMS is widely used for refractory depression, with rTMS being most effective for refractory unipolar depression (i.e. major depression).[15,16] Currently, rTMS is also an approved therapy for migraine in the UK.[16] However, the effects of TMS on cognitive function for patients with specific neurological or psychiatric conditions – such as Parkinson's disease (PD) and bipolar disorder – remain unclear.[31,32]

rTMS provides therapeutic effects by stimulating the brain through the scalp at different frequencies and intervals using a coil to increase or decrease excitability of the motor cortex.[29] The therapeutic effects of rTMS are dependent on the frequency of stimulation pulses, which vary among different types of rTMS, alongside the brain area which is being stimulated and the duration of the procedure.[16] Differences in efficacy have been studied between high- and low-intensity rTMS to facilitate post-stroke clinical recovery, with both shown to be safe, effective, and well tolerated by patients.[29] As a result, rTMS has supported clinical recovery and functional independence in some patients.[8] rTMS has also been reported to be effective for chronic schizophrenia with active hallucinations.[16]

Specific types of rTMS include theta-burst stimulation (TBS), unilateral and bilateral intermittent TBS (iTBS) or continuous TBS (cTBS), deep TMS (dTMS), synchronized TMS (sTMS), accelerated TMS (aTMS), and priming TMS.[8] TBS is the most commonly used type of rTMS for therapeutic purposes.[11] dTMS has been cited to have promise replicating and potentially improving evidence that has been gathered through rTMS for treating obsessive-compulsive disorder.[33]

TMS has also been used or studied to treat ADHD,[19] anxiety disorders,[16] bipolar disorder,[31] epilepsy (including through image-guided TMS)[34,13] essential tremor,[35] fibromyalgia,[9] Parkinson's disease,[36] substance use disorders,[8] choreas,[35] traumatic brain injury,[3] and chronic tic disorders.[11]

Magnetic seizure therapy (MST)

MST is a convulsive therapy with similar effects to ECT, but uses a magnetic field instead of electrical stimulation to induce a seizure. In MST, a magnetic coil is held against the scalp to generate an electric current through a magnetic pulse.[6] Despite being a relatively novel procedure, MST has recently been claimed to be as effective as ECT in clinical trials for major depression, and also induces more localised seizures in the brain than through ECT.[37] Other randomised trials focusing on unipolar depression, bipolar mania, and bipolar depression also indicate high response rates, fewer cognitive adverse effects than ECT, and prospects of MST becoming an alternative therapy for treating refractory mood disorders.[6,38–40] However, there are few clinical trials that compare conclusive interventions specifically for bipolar depression. Evidence of long-term effects and efficacy of MST are currently unavailable.

Pulsed electromagnetic field therapy (PEMF)

PEMF has a similar technical profile to low-intensity rTMS, but has historically been used for pain relief and treating symptoms of orthopaedic conditions, such as osteoarthritis.[41,42]

Low-Intensity Ultrasound

Transcranial focused ultrasound (tFUS)

tFUS is a NIBS technology that can target and stimulate deep brain regions with high precision through transmitting low-intensity ultrasound.[12] It has high spatial resolution and is deemed safe.[43] tFUS has been tested on a range of movement, pain, and psychiatric conditions, with its safety established in pilot trials for epilepsy, chronic pain, and disorders of consciousness.[13] It has also been cited to have promising potential in treating fibromyalgia symptoms.[11]

1.3. Invasive Neuromodulation Technologies

Invasive neurotechnologies usually require surgical implantation of a device to perform stimulation. In the neurotechnologies outlined below, there has been a rise in closed-loop stimulation to treat specific conditions - such as OCD, Tourette's syndrome, neuropathic pain, and complex regional pain syndrome - using neuromodulation technologies.[13,44] As both open- and closed-loop approaches are used, the following list summarises the function of each neurotechnology and provides examples of the conditions they treat, using either open- or closed-loop systems.

Deep brain stimulation (DBS)

Deep brain stimulation (DBS) is an invasive neuromodulation technique that delivers electrical stimulation to different regions of the brain. This entails implanting electrodes into the patient's brain and a neurostimulator underneath their skin.[45] DBS is widely used for specific conditions in refractory patients, such as dystonia, Parkinson's disease (PD), and essential tremor.[46] DBS research has widened to a range of neurophysiological and neuropsychiatric conditions, including but not limited to Alzheimer's disease (AD), mood disorders, OCD, fibromyalgia and tic disorders.[47] Although DBS is most known for treating PD and has shown high long-term efficacy for treatment-resistant patients,[13,35,46,48,49] its adoption remains limited.[44]

In the UK, DBS is considered for patients who have had unsuccessful treatment and severe symptoms from dystonia, Parkinson's disease, and epilepsy.[50–52] DBS was also approved for treating epilepsy in most European countries in 2019 and has since also received FDA approval in the US.[15,35,46] Criteria on treatment-resistance for rare conditions have also led to humanitarian device exemptions (HDEs) in the United States, such as for paediatric patients aged above seven with refractory dystonia, and for adults with refractory OCD.[53,54] Cluster headaches have also been treated with DBS.[46]

Major depression is the most commonly studied psychiatric condition in DBS treatment[48], but sufficient clinical trials are still lacking despite significant evidence of effectiveness.[8] Reports of failed clinical trials and experimental treatments for depression have still shown some capability for DBS providing treatment effects.[44] DBS is still an experimental treatment avenue for other conditions, such as Tourette syndrome (particularly through

closed-loop neurostimulation)[44], refractory substance abuse disorders, generalised anxiety, and post-traumatic stress disorder.[46,48] DBS also remains experimental for treating AD,[55] with limited successful treatment outcomes in dementia more generally.[44] DBS has been reported to have some therapeutic effects for schizophrenia, but clinical trials are ongoing.[35]

Despite the potential of DBS to mitigate symptoms in numerous conditions, there have been calls for it to be provided only to patients with treatment-resistant conditions and only by multidisciplinary teams.[48] An example of a multidisciplinary team would include clinicians from a range of disciplines with experience with DBS, as well as the condition being treated, including neurologists, neuropsychologists, and neurosurgeons.

Vagus nerve stimulation (VNS)

Vagus nerve stimulation (VNS) is an invasive neuromodulation technique that electrically stimulates the vagus nerve and sends signals to the brain.[45] Electrodes are placed on the vagus nerve and are connected to a pulse stimulator that is implanted underneath the patient's skin.[13]

VNS is a widely-used treatment method for refractory major depression and epilepsy.[13,34,49] VNS has also been tested for other conditions, such as refractory OCD and bipolar disorder. However, it has not been deemed to have high effectiveness for OCD, partially due to a lack of sham-controlled studies.[33] Its potential has been acknowledged in the context of bipolar disorder, alongside DBS, as possible alternatives that "could overcome some of the challenges associated with the clinically complex presentation of bipolar disorders in difficult-to-treat patients".[45]

Spinal cord stimulation (SCS)

SCS is a neuromodulation technology where target areas are stimulated through electrodes that are placed on corresponding areas of the spinal cord.[13] SCS can be delivered through tonic, burst, and high-frequency waveform patterns.[51] Burst SCS has shown particular effects in pain relief and has minimized side effects when compared to traditional SCS.[52] SCS has been investigated for improving gait impairments due to PD,[13] as well as for the treatment of chronic pain (including neuropathic pain) and complex regional pain syndrome.[13,15]

Dorsal root ganglion stimulation (DRG-S)

DRG-S is similar to SCS, in that the devices are implanted in the same areas, but DRG-S targets the dorsal root ganglion – a specific region of the spine – to treat various types of chronic pain.[58,59] However, its effectiveness may differ depending on the condition that it is used to target. For example, a randomized control trial held between 2018 to 2021 found no significant differences between placebo and DRG-S stimulation for treating chronic pain after lumbar spine surgery.[60]

Responsive neurostimulation (RNS)

RNS is a neurotechnology which records intracranial EEG patterns to begin stimulation. It has been used to treat patients with refractory epilepsy and is a widely used closed loop therapy.[61]

1.4. Brain-Computer Interfaces (BCIs)

Brain-computer interfaces (BCIs) are systems that translate commands sent through brain signals into an action.[62] In most systems, brain signals are measured using EEG then processed by the BCI.[62] The strength of an EEG signal associated with a BCI's function is dependent on changes of activity, which can enhance, reduce, or stop the strength of the ongoing signal.[63] BCIs can also be combined with different imaging or modulation neurotechnologies to optimise patient benefit for specific conditions.[15] Many BCIs are also combined with advanced artificial intelligence (AI) algorithms, such as to provide AI-informed stimulation parameters for a range of therapeutic applications.[64]

There are different ways in which BCIs can be categorised, such as based on the level or type of activity that impacts brain activities, input signals, processing method, invasiveness, or BCI purpose, among others.

BCIs can have active, reactive, or passive systems – or means of collecting information – to perform their intended functions.[63] In an active BCI, results are independent from external stimulants and results stem from voluntary, controlled activities of the brain. Where brain signals react to external stimulants, which in turn impact how a BCI is used, the BCI is considered to be reactive. When the information obtained is involuntary – or unintentional – the BCI is considered to be passive. For stroke and other associated neurodegenerative symptoms, patients would likely benefit most from BCIs that detect brain neural symptoms instead of relying on neuromuscular attributes to deliver intended commands.[65,66]

BCIs can have open-loop, closed-loop, or hybrid feedback systems. There is no user feedback required for an open-loop system BCI to perform its intended functions, whereas closed-loop systems rely on continuous analysis of brain processes to perform modulation activities.[67] Hybrid systems can have diverse input signals from a mix of open-loop and closed-loop sources, combining a range of neuroimaging and neuromodulation techniques to achieve an intended function.[68]

BCIs can also be endogenous and exogenous depending on the nature of the input signals that a given BCI uses.[63] Exogenous BCIs rely on brain activities that react to external stimuli and their features, whereas endogenous BCIs are not impacted by these factors. Instead, they only rely on the brain's self-controlled activity.

BCIs can also be categorised based on their purpose, such as restoring or mitigating emotional-cognitive, motor, and sensory functions.[69] There are individuals who do not need BCIs as interventions for sensory or cognitive functions, but who may need

assistance due to disrupted connections between the brain and their musculoskeletal system. For example, individuals with tetraplegia may use motor BCIs to control the movement of their limbs – including prosthetics, an exoskeleton, or technology to restore or initiate communication and movement. BCIs use and decode brain signals to prompt actions such as typing or movement.

Whether a BCI is dependent or independent is also a determining factor for meeting output goals. For example, it has been noted that independent BCIs would likely be most appropriate for amyotrophic lateral sclerosis (ALS) treatment. This is because independent BCIs do not depend on CNS outputs to perform certain actions.[70] Instead of requiring muscle activities, which would be difficult in ALS due to loss of spinal motoneurons, brain signals would be sufficient to initiate activity. It was also noted that such BCIs would help with communication and movement as assistive rather than rehabilitative technologies.[71]

Another type of BCI focuses on restoring or enhancing sensory functions through providing electrical input to a given device. One example of a sensory BCI is cochlear implants for individuals with hearing loss. However, BCIs used as interface technologies to restore hearing have not necessarily been accepted as necessary or favourable given the alternative, existing communication means for individuals who are hard of hearing, as well as community associations to having hearing loss.[15]

As with other neurotechnologies, a BCI's level of invasiveness is determined based on where brain signals are acquired, alongside where electrodes and neurorecording devices are placed. However, there are mixed classification systems between the two. For example, while the UK RHC's taxonomy would likely categorise an ECoG-based BCI as invasive,[4] other sources would categorise this as a semi-invasive or minimally-invasive BCI depending on the level of anatomical trauma caused by the surgical intervention.[72,73] Invasive BCIs – which include those that may be categorised as semi-invasive – have particularly shown promise in mitigating neurological symptoms following cervical spine injuries,[69] especially for neuromuscular symptoms.[65,66] Both invasive and non-invasive BCIs have been noted to have promising effects on treating quadriplegic cerebral palsy.[65,69]

1.5. Neural Stem Cells (NSCs)

NSCs have been studied for the potential treatment of a range of neurological conditions. They have high regenerative potential, can self-renew, and can differentiate into different types of cells to provide neurohabilitative benefits.[55,74] NSCs include embryonic stem cells (ESCs), mesenchymal stem cells (MSCs), brain-derived neural stem cells, and induced pluripotent stem cells (iPSCs) – which have all been studied for AD treatment.[75] MSC treatments have particularly shown therapeutic efficacy,[76] but they have also shown a low MSC survival rate, alongside other limitations present in other NSCs,[77] such as irrational differentiation.[55] These potentially beneficial indicators and challenges are also applicable to Huntington's disease, Parkinson's disease, ischemic stroke, traumatic brain injury,

ALS, multiple sclerosis, and spinal cord injury (SCI), given previous targeted treatments through stem cell therapies.[55,76]

NSCs have been researched as possible therapeutic interventions for facilitating SCI functional recovery through replacement of damaged CNS cells. MSCs have also been tested in clinical trials, but clinical outcomes did not yield high success rates.[79] Stem cell therapy using ESCs has also been used to target traumatic brain injury symptoms.[76]

NSCs have also been used to facilitate cell repair and cell development for patients with ALS.[76,77] NSCs can help improve overall function that is minimised or lost, such as movement or communication.[80]

The effects of NSCs have also been examined for treating PD symptoms, with ESTs currently being tested in clinical trials.[55] However, results of improvement have been inconsistent despite indications of neurogenesis through EST usage.[76] iPSCs are also expected to provide therapeutic benefit for PD, but regulatory criteria for clinical applications have not yet been determined.[81]

2: Device Obsolescence

One of the aims of this review is to identify and summarise neurotechnologies that were developed or were in active use between 2013 and 2024 but that are now obsolete. The literature search for this review did not yield any groups of neurotechnologies that have become obsolete to date. However, there are devices that perform neuromodulating activities that have become obsolete. This has had serious health impacts for research participants, patients, and other individuals requiring such devices for therapeutic purposes.

Key points:

- Neural device obsolescence refers to implants that have become outdated or that stop functioning. Obsolescence may be planned, stratified, or due to limited funding.
- Device obsolescence often leads to device explantation and abandonment, which involve the removal of implants that stimulate brain or nerve activity.
- As numerous neuroimplant manufacturing companies have dissolved or have abandoned specific devices, there has been a growing concern about involuntary device obsolescence by patients, doctors, researchers, and research participants.
- Device abandonment has become a concern within neuroethics and research ethics, particularly with regards to post-trial access of the implant. A multidisciplinary expert group proposed a consensus definition of this phenomenon in the context of post-trial access in April 2024, with the goal of reducing or preventing its occurrence.
- Some patients faced with device obsolescence opt for DIY ("do-it-yourself") options to try and resolve continued device access.
- Home treatment using neurotechnology has become increasingly available through direct-to-consumer ('DTC') means and approved research trials, including through the Cumulus study in the UK to provide support for patients living with dementia.
- Obsolescence impacts individuals disproportionately based on location and socio-economic means, which causes challenges in balancing technological innovation, financial interests, and equitable access.

2.1. Defining Obsolescence

Neural device obsolescence refers to implants that have become outdated or that stop functioning. Obsolescence can be caused by the device's manufacturing company no longer producing the device or its parts, the device becoming unusable due to requiring upgrades, or the maintenance required to continue device effectiveness becoming unavailable in a given location. Obsolescence may be planned, stratified, or due to limited funding. Planned (or 'built-in') obsolescence is a deliberate strategy to design and produce a device, part, or software with a limited lifespan.[82] This renders the device ineffective or unusable without updating the part that has become obsolete.[83] Stratified obsolescence entails a technology or its parts becoming obsolete in one location but not

another.[84] Funding limitations can occur due to a range of factors, such as company bankruptcy.

Device obsolescence often leads to device explantation and abandonment, which are terms used to describe the removal of implants that stimulate brain or nerve activity.[85] In the literature, device obsolescence and abandonment are sometimes used interchangeably when these are caused by decisions of the manufacturing company. Device explantation and abandonment are also sometimes used interchangeably when initiated by the patient or research participant. However, device removal initiated by patients or research participants is often involuntary due to social, economic, and/or research expectations.

One cause of neural device explantation, obsolescence, or abandonment is a lack of availability of the neurotechnology or its parts. For example, if the manufacturer of a given device dissolves or no longer produces such a device, the device is rendered obsolete. The consumer or patient may need to explant the device as it can cease to function, may not be fixed if malfunctioning, or may cause health issues if used long-term. Similarly, if a company requires upgrades to a device's parts or software, but the consumer or patient is unable to cover these costs, they may also need to explant the device. Lastly, research participants may be expected to have the device explanted at the end of a clinical trial. Even if they keep the device, they are not guaranteed long-term maintenance, and the device can become ineffective.

Device abandonment has become a concern within neuroethics and research ethics, particularly with regards to post-trial access of the implant. This was a key area of discussion in the 2023 Summit on Neural Interfaces held by the Royal Society in London. Following the summit, there was a call to provide a formal definition for invasive neurological device abandonment, with the goal of reducing or preventing the occurrence of this phenomenon.[86] Based on a systematic review of existing literature regarding device abandonment and obsolescence, a multidisciplinary expert group (including physicians, scientists, ethicists, and other relevant stakeholders) proposed a consensus definition, which was published in April 2024. This definition proposes that device abandonment entail at least one of the following:

1. *"Failure to provide information relevant to (the existence or absence of) plans for medical, technical, and/or financial responsibility as fundamental aspects of patient consent during and after a clinical trial.*
2. *Failure to fulfill reasonable responsibility for medical, technical, and/or financial support prior to the end of an implantable device's labelled lifetime.*
3. *Failure to address any immediate needs (e.g., infection or device programming) of the individual using the implanted device, which may result in safety concerns and/or the deterioration of device effectiveness.*
4. *Failure of a clinical research trial if or when:*
    i. *informed consent has failed to address ongoing access to and management of the implanted device (per 1) and/or such other*

devices that may be demonstrated as having equal or greater therapeutic value in the future; and

ii. *individuals responsible for the trial have not made a reasonable effort to facilitate continued access to device and support for patients who benefit from the device."*[86]

2.2. Obsolescence Impact on Health and Access

Device obsolescence may cause a range of accessibility concerns and cause adverse health impacts for individuals who depend on neurostimulation to experience symptom relief. This is a growing concern for patients, doctors, researchers, and research participants, as numerous neuroimplant manufacturing companies have dissolved or have abandoned specific devices.[87,88]

Prospective patients and clinical trial participants face significant risks from surgery, both for implantation and explantation of invasive neurotechnologies. Explanting a functional device within its lifetime or clinical trial would only be expected if other clinical risks were to arise. Despite this, there are published examples of cases of involuntary obsolescence, including one patient who trialled an experimental BCI in 2014 for regaining mobility but was told to temporarily explant their device by the manufacturer due to funding difficulties and to re-implant it once funding would be re-obtained.[89] Given the risks of surgery and financial uncertainty, the patient did not accede to this request. However, they opted to abandon the device in 2021 due to an unrelated event that risked their health, namely developing a severe infection that drove the device's cable into their scalp.[89]

There have also been cases where individuals have opted against removing their obsolete implants specifically because of the risks of surgery,[90] even though keeping these devices could prevent access to other medical treatments. For example, some patients with bionic eye implants risk significant medical complications if they undergo an MRI scan, due to interference between their implant and the neuroimaging technology.[91] These risks have called for transparency on side effects and ongoing availability of medical care to safeguard patients and research participants. In 2022, a patient shared their experience of having an implantable device and experiencing side effects. They had concerns over proceeding with their doctor's advice to undergo an MRI scan due to the potential for it to interfere with the device and cause health risks.[91] Although they reached out to the manufacturing company to clarify the risks and treatment options, they did not respond and the patient had to opt for a CT scan. The company eventually dissolved without warning any of their patients who had been implanted with neurotechnological devices.[91] The patient has expressed their concern at being unable to rule out a brain tumour as they cannot safely undergo an MRI due to still having their implant, which is now obsolete.[91]

Apart from unexpected obsolescence caused by a device manufacturer's financial circumstances, planned obsolescence remains a widespread phenomenon that can limit long-term access and cause subsequent health risks. Policy developments in the UK have addressed planned obsolescence and its impact on electronic waste (e-waste). One

of the goals of the 2019 Electronic Waste and the Circular Economy Inquiry focused on investigating the UK's e-waste industry and built-in obsolescence,[92] i.e., a deliberate strategy used to incentivise customers to purchase a new device, device part, and/or software update by limiting its lifespan.[93] This directly relates to neurotechnology given the risks that many patients face due to planned obsolescence, as well as the contribution that obsolescence of parts, batteries, or whole devices have on e-waste. A well-known example of planned obsolescence is the design of many batteries for electronic devices with short lifespans.[82] The replacement of DBS batteries in the mid-2000s has been cited as a likely marketing decision, whereby the lifespan of batteries was decreased to increase profits, without considering the patient safety risks that severely ill patients would be subjected to by undergoing more frequent surgeries than necessary to replace the batteries.[94]

Notwithstanding risks of infection and anaesthesia due to increased surgical interventions, planned obsolescence also creates significant difficulties for those unable to afford device updates or replacements. For example, an eight-year old who relied on a cochlear implant to attend school with their peers was subject to their implant's model being discontinued by the manufacturing company, requiring their family to purchase a "compulsory upgrade" – which they could not afford.[84] When interviewed about this difficulty, the family commented that, "New machines are so expensive. If we somehow even get another one by gathering money from somewhere, who will give us the guarantee that this will not happen again and again? We are helpless."[84] Although such patients may resort to purchasing devices through direct-to-consumer (DTC) options, this may not provide wide-scale access due to costs beyond their socio-economic means. This reflects the disproportionate impact of planned obsolescence on individuals with limited socio-economic means and highlights the challenge and tensions at play in balancing technological innovation, financial interests, and equitable access.

To mitigate the effects of obsolescence on health and accessibility, there have been calls for standardising neurostimulation device parts. In a 2021 survey, there was strong support (86%) for standardisation of neurostimulation device connectors among surgeons who implant neurostimulation devices.[95] It has been noted that medical device standardisation for neurotechnologies is not a novel avenue. Standardising such parts would follow existing protocols and precedents of medical device standardisation, which has been applied in the context of cardiac pacemakers since the 1990s.[95]

In the absence of guaranteed long-term access to devices and their parts, some patients have resorted to 'do-it-yourself' (DIY) options to attempt continued access. DIY neurostimulation is an existing phenomenon for devices used at home, however it usually refers to the purchase and use of direct-to-consumer ('DTC') neurotechnologies, such as wearable tDCS devices.[96] Although some individuals who wish to continue using their devices may find alternative companies or products that support their implants, others must turn to unsafe measures to attempt continued access. A patient repairing their own device that is not designed for home usage can be considered a form of "involuntary" DIY that stems from necessity, whereby either fixing the device themselves or keeping an obsolete device could pose high associated risks. For example, a patient with a spinal-

cord stimulator that helped with their chronic pain who could not find suitable replacements after the device became obsolete repaired the faulty parts themselves on several occasions by using their skills as an electrical engineer.[97] Eventually, they found suitable and easily accessible parts to repair their device in the United States, which were later discontinued, causing the patient to seek custom-made replacements from China.[97] This has been the experience of many patients with obsolete devices, who have turned to friends living abroad or the informal economy of social media groups to buy spare parts from third-parties.[84] These challenges have prompted discussions on the right to long-term access and considerations on the impact of neurotechnologies on personhood as part of neurorights. This is explored more thoroughly in Section 5 of this review.

Although many patients may resort to unsafe practices and involuntary DIY to ensure long-term access to treatment, there have also been increased efforts to widen access through voluntary DIY options – encompassed by the planned choice to use neurotechnology at home. This has included both DTC devices as well as access through research initiatives. However, there could be limited voluntariness even in DIY use that has originated out of choice rather than economic or accessibility-related pressures. Although DTC devices could be purchased as a planned and voluntary DIY option, there is no guarantee of continued access as companies may still embed built-in obsolescence of parts or experience financial constraints that can lead to the manufacturing company's dissolution.

There have also been concerns that some DTC devices, while available to purchase, may not always reflect research findings on the effectiveness of neuromodulation for specific conditions and thus provide limited therapeutic benefits. For example, there have been mixed findings regarding TES effectiveness across studies, such as tDCS for treating depression.[9,15] Despite this, many DTC tDCS devices for therapeutic purposes have been widely available in the European Market over the last decade, including as portable devices in the UK.[15] Due to these concerns, there have been increased efforts to embed robust research findings prior to marketing some DTC devices. For example, the Flow tDCS device that is available in the UK has been developed and supported through over 10 double-blind, placebo-controlled clinical trials – which indicates reliable and well-informed study findings.[15]

Another example of a recently approved device, which was developed in the UK, is an AI-powered wearable device that tracks brain activity and cognitive performance, which is aimed at assisting remote tracking of the patient's health to complement the treatment of a range of neuropsychiatric conditions.[98]

Home treatment using neurotechnology has also become available through approved research trials. In the UK, the Cumulus (CNS-101) study started in 2022, aiming to "investigate whether measurement of multiple neurocognitive functions can be done in home by people living with dementia" using a tablet and a wearable headset that records brain signals through EEG.[99] It is intended to:

1. Enable more frequent measurement in a familiar, comfortable setting for people living with dementia, who otherwise would have to attend multiple, in-person clinic visits of lengthy duration.
2. Allow for repeated measurements over time, with the potential to increase our understanding of disease progression and response to treatment.
3. Save time and costs on brain assessments.
4. Accelerate the progress of clinical trials that are testing new therapies for dementia.[10]

There are several study sites across the UK and the study was approved for a period of 2 years, ending in 2024.[99,100] At the time of writing, the study was ongoing and findings were pending.

3: Legal, Policy, and Regulatory Developments

Between 2013 and 2024, governance of neurotechnology regulation and access has shifted due to Brexit, neurotechnological developments, and the Covid-19 pandemic.

Key points:

- Since Brexit, the regulation of medical technology ('medtech') in the UK has been governed by the Medicines and Medical Devices Act 2021. Northern Ireland is subject to both EU and UK regulations on medicines and medical devices.
- Since May 2020, the regulator for medical devices and upholding the UK MDR in the UK has been The Medicines and Healthcare products Regulatory Agency (MHRA)
- UK regulations on medical devices include the Medical Devices Regulations (MDR) and the In Vitro Medical Devices Regulations (IVDR).
- The Regulatory Horizons Council considered the MHRA's scope and proposed a taxonomy of neurotechnologies based on a device's associated level of risk, focused on level of invasiveness and device purpose (i.e. recording or modulation). The recommendations for the MHRA to regulate all neuromodulation devices and only neuroimaging devices that are marketed for medical purposes have been accepted.
- The UK's approach to regulating medical devices closely aligns those of the EU, although support for international alignment has varied.
- The MHRA only allows early access of technologies through the Innovative Devices Access Pathway, introduced in 2022, and for humanitarian reasons for single named patients in exceptional circumstances.
- The Covid-19 pandemic caused significant barriers in accessing healthcare services and neurosurgery, including for neurology and psychiatry services. The MHRA provided large-scale exemptions on granting early access to specific medical devices for a limited amount of time to mitigate the impact of the Covid-19 pandemic.

3.1. UK and EU Law

Prior to Brexit, the regulation of medical technology ('medtech') in the UK was aligned with the European Union (EU)'s regulations as an EU Member State. The EU has competence over Member States' domestic regulations on regulating human medicines and associated clinical trials.[101] The UK was bound to the EU framework for medical device regulation under Directive 90/385/EEC on Active Implantable Medical Devices and Directive 93/42/EEC on Medical Devices.[102] The UK implemented these provisions within national law via the Medicines and Medical Devices Act 2002, but has not been subject to these since 31 January 2020 under the provisions of the European Union (Withdrawal) Act 2018 (EUWA).[103] The Medicines and Medical Devices Act 2021 currently governs all medical devices in the UK.

Currently, UK regulations on medical devices include the Medical Devices Regulations (MDR) and the In Vitro Medical Devices Regulations (IVDR), In the EU, the two directives on medical devices were replaced by the EU Medical Devices Regulations (EU MDR) in 2017 and came into force in May 2021. For in vitro devices, the EU IVDR came into force in 2022. As both were enacted after the UK Exit date, these regulations only applied in Northern Ireland. Data protection was also governed by EU law, which was retained in the UK post-Brexit under the UK GDPR and Data Protection Act 2018.

Since May 2020, the regulator for medical devices and upholding the UK MDR in the UK has been the Medicines and Healthcare products Regulatory Agency (MHRA).[104] The governing UK legislation is the Medicines and Medical Devices Act 2021, which must comply with the EU MDR in Northern Ireland under the Northern Ireland Protocol (NIP). In the UK, medical devices are regulated by the UK MDR 2002 (as amended) and the UK IVDR 2019. In Northern Ireland, the EU MDR and IVDR take precedence over UK regulations only if there are conflicts on areas where the EU has competence.

The new regulations on medical devices have affected the use and regulation of neurotechnology in the UK, prompting a need to define which neurotechnologies fall under the category of "medical devices". The scope of the MHRA's regulation of neurotechnologies was considered in an independent report in 2022 by the Regulatory Horizons Council (RHC). The RHC made regulatory oversight recommendations based on device invasiveness and device purpose (i.e., recording or modulation), and proposed a framework with a neurotechnology taxonomy classification based on a device's associated level of risk.[105] The report calls for all neuromodulation devices to be regulated by the MHRA, irrespective of level of invasiveness or purpose (i.e. therapeutic or non-therapeutic).[105] For neuroimaging devices, the report proposed that the MHRA should only regulate devices marketed for medical purposes.[105]

The RHC recommendations were accepted by the Government in 2024, which confirmed that the MHRA regulates all neuromodulation devices, invasive neuroimaging devices, and only non-invasive devices that *record* neural information for medical purposes.[106]

3.2. Alignment of UK regulation with EU and international standards and practice

Harmonisation with international practices on medical device regulation and safety has been considered at different stages of the regulatory changes described above.

There has been strong public support for aligning the UK's approach to medical device regulation with international standards, and particularly with the EU.[107] In 2021, the MHRA evaluated the extent to which their proposed regulatory framework should align with international practices through a public consultation.[108] There was high support (80%) for alignment with the EU MDR and lower support (56%) for alignment with the International Medical Devices Regulatory Forum (IMDRF).[107] However, it is worth noting that 24% of respondents did not know or had no opinion on alignment with the IMDRF, whereas only 7% of respondents did not know or have no opinion regarding harmonization with the EU MDR.[107] Key areas of support for EU and international harmonisation included: economic

and operational benefits for manufacturers, wider choice for patients, the prospect of manufacturers deeming the UK a more attractive destination, providing clear definitions (including on software) and consistent interpretation of regulations, and favouring a risk-based approach to classification.[107]

Currently, the UK's approach to regulating medical devices closely aligns with EU regulations, which have been supported by the public in the 2021 consultation on this matter. However, support for alignment can vary depending on some matters. For example, in 2018, the Medical Devices Safety Review ('The Cumberlege Review'), addressed how the health system in England responded to reports from patients about side effects from medicines and medical devices and how the Government should respond to these concerns.[109] One of the Review's recommendations, which was rejected by the Government, was to create "[a] new independent Redress Agency for those harmed by medicines and medical devices […] based on models operating effectively in other countries."[109]

There have also been international efforts to address neurotechnology regulation. Several international organisations have made initiatives to develop an international governance framework on neurotechnology.[105] For example, the UK is one of the founding members of the Organisation for Economic Co-operation and Development (OECD), which adopted a legal instrument on Responsible Innovation in Neurotechnology in 2019. This policy document outlines a series of recommendations for both public and private stakeholders to address ethical, social, and legal implications as neurotechnologies advance while promoting innovation, inclusivity, collaboration, safety, and regulatory oversight as key areas of consideration. The OECD has clarified that this legal instrument does not replace regulatory frameworks, but that it can instead help with shaping responsible innovation[110] Between 2017 and 2019, they also published three policy papers on strengthening responsible neurotechnology innovation and issues in neurotechnology governance.[111–113] Although the UK is not legally bound to OECD policy or frameworks, it has contributed to their development as an OECD member.

3.3. UK Government strategy, initiatives, and exemptions

The significance of medtech innovation in developing the UK medtech market, improving health outcomes, and increasing access to new technologies through innovation has been outlined by the UK Government's Medtech strategy.[114] Medtech comprises a significant amount of healthcare expenditure in the UK, with the NHS spending approximately £10 billion annually.[115] In England, £604 million were spent on medtech appliances in community care in 2022.[116] Furthermore, between 2015 and 2022, the UK medical device market was the third largest in Europe, behind Germany and France. As of 2023, it is the fourth largest in Europe – behind Germany, France, and Italy – and eighth in the world, valued at $9.09 billion.[117,118]

In 2024, an update to the Medtech strategy report outlined achievements and further goals to increase medtech innovation, making reference to the Innovative Devices Access Pathway (IDAP) pilot.[119] The IDAP, first introduced in 2022, is a joint project

between NICE, the MHRA, Health Technology Wales, and the Scottish Health Technology Group. The IDAP aims to "offer a supported research and access route for innovative medical technologies and digital devices that meet a critical need in the NHS" and to "[allow] manufacturers to provide their innovative device to healthcare professionals and patients at the earliest, safe, opportunity".[119] Eight products have been approved to date under the IDAP.[120] Although there are no approved neuromodulation or neuro-recording devices, two of the products seek to help with two neurological conditions, namely multiple sclerosis through a fatigue app and stroke identification through a portable diagnostic device.[120]

Other countries have also introduced early access exemptions, such as the U.S. Food and Drug Administration (FDA) Investigational Device Exemption (IDE) and Humanitarian Device Exemption (HDE). To promote flexibility of adopting emerging neurotechnologies and foster innovation, there were proposals in 2021 for the UK to consider developing an 'investigational device' similar to the FDA's IDE process.[98] However, the UK has not to date developed such a pathway other than the IDAP, which is limited to specific products. The MHRA considers the exceptional use of non-UKCA marked/non-compliant medical devices on humanitarian grounds, but this is limited to a single named patient rather than a larger cohort of patients with the same condition(s).[121] Applications for exceptional use can be made by a device manufacturer "to supply a medical device that does not comply with the law to protect a patient's health if there is no legitimate alternative available" and includes in vitro diagnostic medical devices.[121]

UK provisions do not have other humanitarian exemptions, such as the FDA's HDE, which has been used for several neurophysiological and neuropsychiatric conditions to permit neuromodulation access, such as DBS for adult treatment-resistant OCD or paediatric treatment-resistant dystonia.[122] The HDE was established to create a new regulatory pathway for products intended for rare diseases or conditions, which are considered orphan products. It provides this access given that sufficient clinical evidence to meet FDA standards is difficult if the sample size and patient population affected is small. This is different to expanded access for medical devices, which most closely mimics the MHRA's guidance on humanitarian grounds exemptions, and focuses on emergency use, compassionate use, and treatment investigational device exemptions.[123] Although the MHRA reviews applications for orphan designation of medical products, there is no pre-marketing authorisation orphan designation under any of its provisions.[124]

3.4. The impact of the Covid-19 pandemic

The Covid-19 pandemic caused significant barriers in accessing healthcare services, including for neurology and psychiatry services. As some different technologies were difficult to access or procure throughout the pandemic, large-scale exemptions for medical devices were made in the UK.[125] In June 2020, the Government published a list of manufacturers and medical devices granted an exemption by MHRA. This included two models of the Hypoglossal Nerve Stimulation System by Inspire Medical Systems, an implanted neurotechnology that electrically stimulates the hypoglossal nerve to trigger tongue movement.[126] The exemption was issued in March 2021 and expired in

September 2024.[127] This approach was also adopted by other countries, such as the US FDA, which provided approved temporary alternative neurotechnology access to patients with major depression who had difficulties accessing their usual regimen of treatment during the Covid-19 pandemic. For example, the FDA approved a trial of home treatment tDCS usage under an IDE in May 2020, until patients could re-gain access to rTMS and/or ECT.[128]

However, for other neurotechnologies, there were limited means by the impact of the pandemic on access could be mitigated, with patients requiring neurosurgery being particularly affected. In May 2021, Baroness Gale raised a question for a short debate in the House of Lords Grand Committee on the Government's plans to restart specialist neurology services and introducing a national strategy for neurorehabilitation, making direct references to the pandemic's negative effects on neurosurgery and DBS access for Parkinson's disease.[129] The significant impact of the pandemic on neurosurgery access was reflected in the difference between the number of DBS procedures performed in England through the NHS in 2019 compared with 2020: an average of 20 DBS procedures per month in 2019, and only 135 for the whole of 2020.[129]

4: Robust and Diverse Clinical Trials

There have been recurring themes in neurotechnology research on developing standardised protocols in research trials, creating more robust and diverse clinical trials, and setting clear eligibility criteria. Specific concerns have been raised about the involvement of vulnerable groups, including children, in clinical trials and further timely access to treatment. Both research and policy in this area have made calls for providing equitable access and enhancing public and patient involvement to mitigate existing barriers in research participation and clinical access to neurotechnology treatment.

Key points:

- A key emerging theme across the literature pinpoints the need for more double-blind, randomised controlled clinical trials with standardised testing protocols prior to making neurotechnologies available for therapeutic access.
- Using specific combinations of neuromodulation and neuroimaging technologies have been explored to maximise treatment effects and pave the way for personalised medicine for a range of neurophysiological and neuropsychiatric conditions.
- Neuromodulation technologies are predominantly only considered for patients whose prior standard treatment has failed. However, there are gaps in setting consistent inclusive and exclusive criteria in neuromodulation research – such as defining treatment resistance and considerations over the severity of the patient's symptoms.
- Concerns over some study criteria include that some patients who may benefit could be excluded from participation, such as children, patients with comorbidities, or other groups of patients who are deemed to be vulnerable due to their condition(s).
- Further concerns reflect that as health outcomes are impacted by social determinants and to widen access, research trials need to have diverse participants, including children and underrepresented groups in both clinical settings and research. The lack of diverse demographics in research impacts the generalisability of data and can make the effects of novel neurotechnologies less safe for such groups.
- Representation gaps of specific groups throughout the stages of a device's development and usage might also suggest there is a need to explore wider perspectives through patient and public involvement (PPI). The MHRA has expressed its commitment to enhancing PPI in its 2021-2023 corporate plan and its PPI 2020-2025 Strategy.

4.1 Standardised protocols

A key emerging theme across the literature pinpoints the need for more clinical trials to take place on neurotechnology effectiveness for different conditions. For these interventions to be safe and effective, there is a shared view that more double-blind, randomised controlled trials with homogenous testing protocols need to occur prior to

making any such technologies available for therapeutic access. For example, although tDCS has been studied as a potential treatment for ADHD, dyslexia, and autism spectrum disorder, there is a need for more large, randomised, sham-controlled trials and robust experimental designs in paediatric populations.[130]

There are also calls for these trials to have long-term follow up plans to appropriately identify and address benefits or adverse effects of neurotechnologies.[69,131] Important considerations relating to how a given technology may impact a research participant – and a prospective patient – also vary based on: the technology; level of modulation; type of modulation; condition that is being tackled through neurotechnology; the presence of any comorbid medical conditions; and other social and biological aspects that may impact treatment effectiveness, such as age.

Recurring themes in the literature focus on improving the level of scrutiny applied to trials of neurotechnologies that aim to serve as therapeutic alternatives. For example, rTMS may provide an opportunity to personalise treatment protocols for patients with specific manifestations of a given condition.[13] tDSC and TMS have also shown potential for reducing tics in tic disorders, but it has been noted that supporting clinical evidence needs to increase and NIBS parameters need to consider patient personalisation before these technologies become standard treatments.[11]

Specific combinations of neuromodulation technologies (i.e., rTMS, tACS) and neuroimaging technologies (i.e., EEG, MEG) have also been explored as avenues that can maximise treatment effects and pave the way for personalised medicine for a range of neurophysiological and neuropsychiatric conditions.[36,132,133] Similarly, it has also been suggested that the use of BCIs which combine technological inputs – both with recording and modulation properties – and feedback systems also shows promise for personalised treatment.[15] A range of neurophysiological conditions could be treated through BCIs that are used alongside fNIRS, tDCs, other BCIs, and other inputs.[15] This combination, with an extension to include several imaging technologies, has been proposed as an example with therapeutic prospect for treating essential tremor.[15] However, although the likely potential of many neurotechnologies has been noted, and consistent benefits are expected through increased trials, a key concern remains a lack of standard methodology, even for TMS, tDCS, and DBS which are widely used.[33]

Another key challenge identified in the literature relates to the long-term reporting of side effects and neurotechnology effectiveness. This includes the risks of over-stating positive or negative effects of neurotechnologies when reporting findings.[134] Apart from the need to ensure best practice in clinical research, appropriate reporting of effects has also been seen as necessary to prevent unrealistic expectations in clinical trial participation, which can cause unintended negative side effects in vulnerable groups, such as children.[134] Such effects are difficult to generalise in the absence of long-term trials. For example, although many studies have determined that tDCS is a predominantly safe intervention with minimal, mild side effects, this level of safety has only been made for short-term usage given the lack of studies focusing on children, and thus, makes long-term side effects of these technologies on a paediatric population unavailable.[15]

4.2 Eligibility Criteria

Neuromodulation technologies are predominantly only considered for patients whose prior standard treatment has failed. It has also been suggested that non-invasive neurotechnologies be tried prior to considering invasive technologies – such as deep brain stimulation (DBS) – for these patients.[33] However, there have been difficulties in establishing consistent definitions for treatment resistance across research and clinical practice.[135,136] This can make it difficult to determine whether to refer a patient for neuromodulation treatment and to establish whether a research participant meets eligibility for clinical trials for treatment-resistant conditions. These gaps in setting consistent inclusive and exclusive criteria in neuromodulation research – including defining treatment resistance and considerations over the severity of the patient's symptoms – can impact the consistency of clinical trials and patient referrals.[135]

Inconsistent eligibility criteria can also cause concerns over exclusion of certain groups in research. For example, some patients that may benefit could be excluded from participation, such as those with comorbidities. This is a particular concern for patients who experience significant interferences to their quality of life from more than one condition.[33] These patients may experience varying levels of treatment effectiveness from neuromodulation interventions depending on the level of treatment-resistance that they experience with each condition.[135] For example, TMS and ECT have shown effectiveness for some patients with comorbid conditions, such as major depression and obsessive-compulsive disorder.[137–139] However, these findings have been mixed for patients with comorbid treatment-resistant OCD.[33,139–141] Therefore, even though these technologies may be effective for specific conditions, the level of effectiveness may differ depending on the patient's presentation when targeting multiple conditions. This may suggest a need for increased transparency in reasons behind specific eligibility criteria and efforts to standardise them.

Thorough consideration of eligibility criteria could also help ensure that trials consider condition-specific effects from neurotechnology treatment. This is because there may be varying levels of effectiveness across patients who may experience similar symptoms, but which are caused by different conditions.

For example, a 2021 review assessed clinical evidence for the treatment of PD through specific non-invasive neurotechnologies, noting effectiveness of rTMS, tDCs, and tACS.[36] This review noted the promise that NIBS holds for sub-groups of those affected by PD, based on their symptoms, to provide personalised care. Clinical trial results vary, although this can likely be attributed to study populations and study protocols rather than solely effects of specific NIBS on treating PD symptoms. Findings on NIBS usage for PD symptoms however indicate the need to evaluate the relationship between neurotechnologies, specific symptoms, as well as the conditions that cause such symptoms. For example, although TMS may improve the symptoms of depression and motor symptoms in patients with PD, the efficacy of treating other movement conditions is not clear.[30] This can mean that although the same symptoms are targeted, as the cause

of symptoms is different, treatment outcomes may not be as effective. These are areas that can be considered early on in the research process when inclusion and exclusion criteria are set to account for the above circumstances.

Gaps have also been observed in the reporting of inclusion and exclusion criteria for children. For example, despite neurotechnologies holding substantial potential for neurohabilitation for children with refractory neurophysiological and neuropsychiatric conditions, study participants under the age of 18 have not been included on any clinical trials of intracortical BCI and the reasons for exclusion are largely omitted in publications.[69] Exclusion of paediatric populations in research often results in children and adolescents receiving treatment access significantly later than adults. For example, DBS was approved in most European countries in 2019 and has since also received FDA approval in the US.[15,35,46] This includes treatment for children through a humanitarian device exemption.[69] However, this is not the case for RNS, which is an invasive neurotechnology that has encouraging results for epilepsy.[69] It is not currently available to children through such an exemption, which reflects the trend that neuroprosthetic devices become available to paediatric populations significantly later than adults, despite the promise of symptom relief. By contrast, external, wearable devices for epilepsy management are currently being tested in a variety of patient populations, including children.[15]

4.3 Equitable Access and Involvement

Research trials need to have diverse participants to reflect the fact that health outcomes are impacted by social determinants. This includes children and underrepresented groups in both clinical settings and research.[142,143] The lack of diverse demographics in research impacts the generalisability of data and can make the effects of novel neurotechnologies less safe for such groups.[144]

A lack of diverse data can also exacerbate engineering and algorithmic bias for different types of neurotechnologies, including AI-powered or AI-assisted devices. This was addressed in the UK in the *Equity in Medical Devices Independent Review*, which sought to determine the extent and impact of biases in the design and usage of medical devices.[145,146] The review deemed AI a medical device (AIaMD) that could raise bias-related harms at its very inception, noting that, “if those data [used in machine learning] are unrepresentative of minority groups or biased in some other way against population subgroups, the models may ‘learn’ biases engrained in medical practice and exacerbate existing health inequities”.[147]

Furthermore, based on existing reports of such biases and cases of disadvantages to women and ethnic minorities, there have been higher reports of distrust in AI by groups that have been underserved in the field.[147] This distrust makes disadvantaged groups less inclined to seek medical treatment. Those who do opt to use AI-powered devices may also experience adverse effects if devices are not tailored to their needs due to insufficient data and algorithmic biases. Similarly, use of devices with lowered performance or quality can also pose health risks. As outlined in the UNESCO

International Bioethics Committee's Ethical Issues of Neurotechnology Report, this can cause disproportionate barriers to accessing new technologies.[148]

With a growing number of AI-assisted neurotechnologies, such as BCIs, algorithmic bias can cause significant health disparities among different ethnic, racial, and gender minorities. However, inadvertent biases due to engineering decisions also exist in neurotechnologies not powered by AI. This is seen in the reduced efficacy of EEG and fNIRS – two examples of recording neurotechnologies – on individuals with thick, curly hair and dark skin complexions.[149] The Equity in Medical Devices Independent Review also highlighted pulse oximeters as an example of device design that led to varying levels of effectiveness and adverse health effects. Pulse oximeters can be used in neurotechnology applications; for example, as part of anaesthesia protocols, pulse oximetry is applied at the beginning of DBS surgery.[150] As they rely on light to determine the level of oxygen in blood, the efficacy of results can be impacted by a range of factors – such as skin colour. As less precision has been reported in non-White racial groups, this can disadvantage racial or ethnic minorities due to creating higher rates of poorer device performance.[147,151] Having inaccurate readings could thus pose significant concerns of accuracy and disproportionate adverse effects for underrepresented groups across all areas of device development – from inception to application.

A further diversity gap can result from vulnerable populations not always being seen as appropriate research subjects – e.g. due to concerns over genuine informed consent – despite being the populations who may benefit most from certain treatments. For example, despite the fact that there are patients with conditions that compromise movement and communication (such as locked-in syndrome) and who may benefit significantly from BCIs, they are "not the most suitable research subjects" due to concerns that their choice to participate in research is based on unrealistic expectations of benefit and a lack of clinical treatment options, rather than genuine voluntariness.[69] However, this can compromise respect for autonomy and would be contrary to the need to include these groups more actively in clinical research, treatment decisions, and respective policies.

The RHC has highlighted concerns over equitable access to neurotechnology, and requested that the UK Department for Health and Social Care "consider adopting policies to ensure that neurotechnologies are available to a wide patient base regardless of their personal characteristics".[105] Personal characteristics can include those protected under the Equality Act 2010[152] – such as disability, age, race, among others – which could be applied in this area to widen access to neurotechnology research. This is being addressed in the MHRA's work on developing a joint diversity and inclusion guidance with the Health Research Authority, as well as through their validation process for clinical investigations, which requests applicants to outline plans on addressing bias.[153]

These representation gaps, throughout the stages of a device's development and usage, might also suggest there is a need to explore wider perspectives through patient and public involvement (PPI). The Cumberlege Review made a recommendation on the need for the MHRA to increase PPI, raise awareness of its public protection roles, and to ensure

that patients have a key role in the MHRA's work. This recommendation was accepted and the MHRA's recent efforts to adopt these changes were outlined. These included the MHRA's 2021-2023 corporate plan[154] on putting patients first through enhanced PPI, its efforts to transform organisational structure to put patient safety at the forefront of its work,[154] and the MHRA's Patient and Public Involvement 2020-2025 Strategy[155]. The MHRA held a public consultation on this strategy between May and June 2021. The outcome of this consultation has not been published as of October 2024.

5: Neurorights

The impact of therapeutic neurotechnology use and post-trial access on identity, data protection and long-term safety have raised questions over the rights that patients and research participants have in these contexts. This includes considerations associated with personhood, such as personal autonomy (including exercised through informed consent), identity, authenticity, and mental privacy as part of 'neurorights'.[97] Legal and policy developments have considered how patients with neuromodulation implants may have changed perceptions of self, agency and identity, alongside concerns over patients' ability to exercise autonomy authentically post-surgery. In turn, these policy and legal outcomes have impacted how neurotechnology is regulated and used to safeguard patients and research participants.

Key points:

- Neurorights encompass the rights of patients in the context of neurotechnology on a range of areas related to personhood, such as autonomy, integrity, non-discrimination, and privacy. Numerous international efforts have considered whether existing human rights frameworks protect these rights to their fullest extent.
- There have been calls to better consider the experiences of patients who use neurotechnology and the extent to which they deem their implants to impact their identity.
- Ethical implications of neurotechnology usage with regards to privacy and personal data collection have been considered both in the UK and internationally. Some countries have made efforts to enshrine neurorights and provisions on neurodata through legislation and policy measures.
- The impact of neuromodulation use on personhood has also raised concerns about the impact of device obsolescence and explantation on patients' health. There are gaps in the available literature on whether device manufacturers, insurance companies, and/or study organisers who implant neural devices in research subjects have a duty of non-abandonment to research participants, and whether a failure to upload such a duty would entail a breach of an individual's neurorights. The MHRA has made efforts to support long-term implants and access.
- There is a lack of regulatory guidance on whether there should be a continuous informed consent process as part of post-trial access, alongside who should be responsible for seeking and obtaining this.

5.1. Impact of neurotechnology on perceptions of personhood

Neurorights considerations have emerged in the UK and internationally through empirical studies, reports, and legislation.

In 2019, the Council of Europe – of which the UK is a member – published its Strategic Action Plan on Human Rights and Technologies in Biomedicine (2020-2025).[156] The plan referred to the impact that neurotechnology can have on privacy, personhood, and discrimination, with the aim of considering whether existing human rights frameworks protect these rights to their fullest extent. Other priority areas in the plan included equity in healthcare; enhancing underage patients' participation in decision-making on their health; and strengthening long-term strategic cooperation with Council of Europe committees and other intergovernmental bioethics bodies on these matters.

The impact of neurotechnology on perceptions of personhood was also addressed in a 2021 report on Ethical Issues of Neurotechnology published by the UNESCO International Bioethics Committee. Key takeaways focused on the impact that neurotechnologies can have on bioethical and human rights notions of mental integrity, human dignity, personal identity, autonomy, mental privacy, accessibility, and social justice – which can all fall under the umbrella of 'neurorights'.[148]

There have been calls to consider the experiences of patients who use neurotechnology more closely and the extent to which they deem their implants as part of their identity – either because of a perception of themselves changing due to having an implant, or due to side effects of the technology potentially causing changes in their thoughts and behaviour.[86] These considerations have also been identified in patient experiences, including a study that interviewed patients who used BCIs to treat refractory epilepsy symptoms.[97] Although experiences have ranged between perceptions of enhanced levels of freedom to feeling less in control since receiving their implants, the shared experience among participants was that their sense of self was impacted by implanting a BCI.[97] These ethical concerns have surfaced in both BCI and DBS research,[97,157] with some patients reporting increased perceptions over their agency and others feeling a sense of self-estrangement.[158]

5.2. Neuroprivacy and Neurodata

Neurorights discourse has also focused on neuroprivacy (including mental integrity privacy) and the protection of neurodata. These were focus points in the Council of Europe's 2021 report on 'Common Human Rights Challenges Raised By Different Applications of Neurotechnologies in the Biomedical Field'[159]. Questions over privacy, autonomy, agency, and justice were used as key lenses to address the legal, social, and ethical implications of neurotechnologies. These included mental integrity and the right to privacy in light of potential breaches that can be facilitated through neurorecording and neurostimulation. Rights such as freedom of thought, private life, and privacy were linked to existing human rights that are binding in the UK, such as the Universal Declaration of Human Rights[160] and the European Convention on Human Rights[161].

UK context

The UK Information Commissioner's Office (ICO) published a report on neurotechnology in 2023.[162] It highlighted the following ethical implications of neurotechnology usage with regards to privacy and personal data collection:

- neurodata can pose risks to information rights;
- there is a risk of transparency breaches from organisations based on their access and usage to sensitive data gathered through neurotechnologies;
- neuroprivacy and neurodata do not have formally accepted definitions;
- neurodata, while it may be protected under the notion of mental integrity protection, is not specified in law (including soft law) or regulation; and
- neurodata is not defined as a special category under the UK GDPR, although it may be considered as such if collected and processed for medical purposes.[163]

There have been calls for further consideration of the ethical concerns and patient experiences relating to neurotechnologies and the protection of patient rights and neurodata. In 2022, the RHC Independent Report noted that the spike in neuromodulation usage will amount to collecting substantial amounts of personal "neurodata" from users.[105] The RHC requested that the ICO should clarify how this type of data collected is covered under provisions of UK data protection law.[105] The Government accepted this recommendation, noting the ICO will develop specific guidance on neurodata by 2025.[106]

International context

The status of neurodata within the regulation of data protection has been addressed in numerous countries through extant legislation and policies on neurorights. For example, Spain's Charter of Digital Rights outlines specific rights and provisions subject to legal regulation in the usage of neurotechnologies – including BCIs – to guarantee self-determination, equality, non-discrimination, and dignity.[164]

Similarly, in 2023, the Chilean Supreme Court discussed the right to mental privacy with respect to neurodata, including whether the latter is protected and considered personal data.[165] Although there has been no formal stance or application into law on the status of neurodata, the notion of neuroprotection in medical contexts has been included in Article 19 of the Chilean constitution,[166] which the ICO noted was 'the first explicit piece of legislation directly about neurodata' after it was proposed in 2020.[1]

There have also been a number of attempts or proposals to incorporate neuroprivacy and neurodata into legislation in other countries. In 2021, a draft bill in Brazil proposed that "neural data constitutes a special category of sensitive health data that requires greater protection".[166] As part of protecting neurodata as personal data, the bill further proposed to only allow neurodata processing with explicit consent and to prohibit neuromodulation usage in any manner that "could harm someone's identity, autonomy or psychological continuity, as well as communication between data controllers or their joint use of neural data aimed at obtaining economic benefit".[166] Other jurisdictions have explored the

neuroprotection and the regulation of neurorights more widely. For example, a draft bill was introduced in 2023 in Ecuador to address the ethical applications of both invasive and non-invasive neurotechnologies.[166] This predominantly focused on protecting human dignity, physical and mental integrity, neural data privacy, autonomous decision-making, and the right to non-discrimination.[166] It echoes the content of other draft bills proposed in Mexico in 2024 and in Argentina in 2022, the latter also specifying that any usage of personal information stemming from mental activity (i.e., brain functions) should provide information on its purpose and scope.[166] There has not been further approval or implementation of these initiatives at the time of writing of this review.

5.3. Neurorights, post-trial access and obsolescence

The impact of neuromodulation use on personhood has also raised concerns about the impact of device obsolescence and explantation on patients' health. As discussed above, there are gaps in the available literature on whether device manufacturers, insurance companies, and/or study organisers who implant neural devices in research subjects have a duty of non-abandonment to research participants, and whether a failure to uphold such a duty would entail a breach of an individual's neurorights, such as autonomy and integrity.[167]

Many patients with BCI implants have expressed a level of "human-machine symbiosis".[158] Two patient participants, with different implants, have been among those who have shared their sense of loss and devastation in the face of device obsolescence due to a lack of continued post-trial access,[84 168] with one describing the removal as being "against their will".[168] Similarly, with the potential for neuro-implants to form a significant part of a patient's identity, the request of device manufacturers or clinical trial organisers for patients to explant devices at the end of a trial has been compared to "removing something constitutive of the person against their will".[168]

The ethics of forced explantation have been increasingly explored through a neurorights lens, particularly informed consent and the right to mental integrity, which are considered to be breached through forced device explantation.[158] To reflect this point, the ethical implications and human rights breaches of mandatory explantation have been compared to those of forced implantation, which would hold a high level of moral objectionability.[85] Consequently, there have been calls for device manufacturers and clinical trials to be considered to have a duty of non-abandonment to patients and research participants.[169] This would include preventing manufacturing companies from unilaterally withholding long-term access to an implanted device – particularly when the key motivation of obsolescence is due to financial constraints.[158]

The responsibility for providing post-trial access in the case of device obsolescence was addressed in the Regulatory Horizons Council's 2022 report. Aiming to propose measures for supporting long-term implants, the report acknowledged persisting and unresolved issues around post-trial access of neurotechnological devices. It recommended the clarification and strengthening of requirements for device manufacturers, requiring them to implement a robust post-market surveillance system:

"[T]he MHRA should consider requiring manufacturers to present a plan describing how they intend to manage long-term implants installed in patients, as part of their submission to Approved Bodies. The plan should capture:

1. *the commitment of the manufacturer to repair, upgrade or remove the device (including software) as required,*
2. *specific instructions on how to maintain and remove the device that can be followed by a third-party in case the company folds; and*
3. *detailed description of arrangements for long-term monitoring of adverse events in a post-market phase.*

The MHRA should also ensure that it has adequate resources to ensure post-market vigilance and to intervene and mediate when a company folds and a handover of responsibilities must be organised."[105]

The MHRA has not, to date, addressed provisions regarding long-term plans that account for a company's financial restrictions. It has developed provisions to support long-term device access by requiring device manufacturers to retain documents for the expected lifetime of a medical device, or for at least 15 years for implantable devices and 10 years for non-implantable devices.[170] However, a medical device's lifetime can often be shorter than that of a patient, and this can therefore still leave some patients vulnerable to obsolescence. Furthermore, retention of documents does not guarantee the same level of expertise or device optimisation for novel neurotechnologies if the device were to be made obsolete. This is a challenge, as a company's long-term financial prospects are not evaluated by the MHRA or other regulators to determine whether to approve a device or clinical trial. Nevertheless, arguably these concerns require due consideration to ensure that patients are safe and have continued access, but also because it is a key component in providing informed consent. There may be research participants who would be unwilling to receive an implant if they were aware of the long-term financial prospects of the manufacturing company, and there have been calls for study sponsors to confirm post-trial support and risks in the informed consent process.[171]

Post-trial device access and long-term plans have also raised issues relating to informed consent. There is a lack of regulatory guidance on whether there should be a continuous informed consent process as part of post-trial access, and who should be responsible for seeking and obtaining this consent. In a 2022 study that examined 44 stakeholder perspectives on trials for implantable neural device trials, researchers noted concerns over the extent to which patient-participants understood provisions regarding post-trial access to the device that they agreed to have implanted.[88] With respect to patient-participants' recollection, 8 of the 21 patient-participants did not recall conversations on post-trial coverage in the pre-surgery interviews, and roughly the same number did not recall such discussions occurring as part of the post-surgery interview six months later.[88] This may suggest a need for more robust informed consent processes and ongoing efforts to provide support to research participants once a trial has finished.

Conclusion

There have been substantial developments in neurotechnology research and use over the last decade. As these technologies become increasingly viable, there is, arguably, a pressing need to address regulatory and policy considerations proactively. The UK has established a taxonomy for neurotechnologies used for medical purposes, which aligns with overarching recommendations on regulation of medical devices. However, neurotechnology categorisations remain diverse across disciplines and countries. There are numerous ethical considerations that need to be continuously addressed and mitigated as these technologies progress, such as: protection of patients and research subjects; considering definitions and protections of neurorights; viability of universality of parts for medical devices; increased PPI across all realms of neurotechnology, including but not limited to production, access, research, and policy; balancing innovation and safety; and robust research and long-term monitoring.

Glossary

The following list of abbreviations and definitions is not exhaustive. It focuses on terms that are used throughout the review.

Definitions of abbreviated neurotechnologies most used in the review:

BCIs - Brain-computer interfaces are systems that translate commands sent through brain signals into an action, often used to restore or mitigate emotional-cognitive, motor, and sensory functions. Many BCIs are also combined with advanced artificial intelligence (AI) algorithms and other neurotechnologies.

DBS - Deep brain stimulation is an invasive neuromodulation technology that delivers electrical stimulation to different regions of the brain. It is widely used for specific conditions in treatment-resistant patients, such as dystonia, Parkinson's disease (PD), and essential tremor. DBS research has widened to a range of neurophysiological and neuropsychiatric conditions.

ECT - Electroconvulsive therapy is a non-invasive convulsive therapy which induces a generalised seizure to create therapeutic effects.

EEG - Extracranial electroencephalography is a non-invasive neuroimaging technology that measures electrical activity in the brain.

Invasive stimulation: Invasive neurotechnologies usually require surgical implantation of a device to perform stimulation.

NIBS – non-invasive brain stimulation and non-invasive neurotechnologies stimulate the brain or nerves externally. They do not require surgery or implantations.

RINCE - Reduced impedance non-invasive cortical electrostimulation is a non-invasive neurotechnology that uses electrical stimulation.

RNS - Responsive neurostimulation is an invasive neurotechnology which records intracranial EEG patterns to begin stimulation.

tACS - Transcranial alternating current stimulation is a mode of TES that involves direct delivery of alternating currents to modulate excitability in the cortex.

tDCS - Transcranial direct current stimulation is a mode of TES that generates a low-intensity, continuous current to stimulate the brain.

TES - Transcranial electric stimulation is a non-invasive neuromodulation technology that stimulates the brain by using an electrical current.

TMS/rTMS - Transcranial magnetic stimulation/repetitive transcranial magnetic stimulation (non-invasive).

VNS - Vagus nerve stimulation is an invasive neuromodulation technique that electrically stimulates the vagus nerve and sends signals to the brain.

The following are abbreviations for most types of neural stem cells.

ESCs – embryonic stem cells are cells that can differentiate into any cell type in the body.

iPSCs – induced pluripotent stem cells are cells that can be derived from skin or blood cells and have the ability to differentiate into many different cell types.

MSCs – mesenchymal stem cells are a type of stem cell that can differentiate into many different cell types.

NSCs – neural stem cells are multipotent cells that can self-renew and generate new neurons and types of cells, which can be used in neurohabilitation to mitigate or restore loss function.

The following are definitions of recurring terms relevant to this review's key research questions.

DTC – Direct-to-consumer neurotechnology access refers to the ability for patients or consumers to directly purchase neurotechnology devices without going through the healthcare system or research participation. These devices can be marketed to have medical purposes or not. Some devices can provide therapeutic benefit.

IDAP – the Innovative Devices Access Pathway (IDAP) pilot is a joint project between NICE, the MHRA, Health Technology Wales, and the Scottish Health Technology Group established in 2022 to increase innovation while providing early access to specific technologies to meet critical needs in the NHS.

Involuntary DIY – DIY stands for "do-it-yourself". in the context of neurostimulation, a patient repairing their own device that is not designed for home usage can be considered a form of "involuntary do-it-yourself" that stems from necessity to maintain a neural device.

IVDR – this stands for the In Vitro Medical Devices Regulations, which regulates in vitro medical devices in the UK. If specified as EU IVDR, it refers to the EU equivalent of these regulations. In vitro devices are regulated by the MHRA.

MDR – this stands for the Medical Devices Regulations, which regulates medical devices in the UK. If specified as EU MDR, it refers to the EU equivalent of these regulations. Medical devices are regulated by the MHRA.

MHRA – the Medicines and Healthcare products Regulatory Agency is the regulator for medical devices and upholding the UK MDR and IVDR.

Neural device obsolescence – refers to implants that have become outdated or that stop functioning. It can be caused by the device's manufacturing company no longer producing the device or its parts, the device becoming unusable due to requiring upgrades, or the maintenance required to continue device effectiveness becoming unavailable in a given location.

Planned obsolescence – a deliberate strategy to design and produce a device, part, or software with a limited lifespan.

RHC – the Regulatory Horizons Council is a body that has made regulatory oversight recommendations in an independent report on neurotechnology regulation in 2022. It proposed a taxonomy of neurotechnologies based on device invasiveness and device purpose. It also made recommendations on the scope of the MHRA's regulation of neurotechnologies.

Stratified obsolescence – a term describing the obsolescence of products in one location while remaining accessible in another location.

Voluntary DIY – DIY stands for "do-it-yourself". In the context of neurostimulation, is an existing phenomenon for devices used at home directly by the patient or consumer.

The following is a list of specific neurological, neurophysiological, and neuropsychiatric conditions that have been abbreviated in the review.

AD – Alzheimer's disease is a progressive neurological condition and a form of dementia that is caused by damaged nerve cells in the brain.

ADHD – Attention-deficit/hyperactivity disorder is a neurodevelopmental disorder that affects a person's behavior and can cause difficulty with attention, hyperactivity, and impulsivity.

ALS – Amyotrophic lateral sclerosis is a rare, terminal disease that causes the progressive loss of motor neurons in the brain and spinal cord. This leads to muscle weakness, loss of muscle mass, and an inability to control movement. ALS is also known as motor neurone disease or Lou Gehrig's disease.

ASD – Autism spectrum disorder is a neuropsychiatric condition that affects how people communicate, interact with others, learn, and behave.

OCD – Obsessive-compulsive disorder is a psychiatric condition that causes people to experience unwanted thoughts and repetitive behaviours.

PD – Parkinson's disease is a progressive neurological condition that causes movement

SCI – Spinal cord injury.

Appendix - Methodology and Research Approach

Research Questions

The guiding questions of this report included the following:

1. What neurotechnologies are in use today, and how are they used?
2. Does the taxonomy of neurotechnologies identified in the 2013 report encompass those that are in use or in development today?
3. Which neurotechnologies have become obsolete in the last decade, and why?
4. What impact have UK policy, legal or regulatory developments over the last decade (including recommendations from relevant independent inquiries) had on the development, application or obsolescence of neurotechnologies?

Methodology and Approach

This review used a qualitative semi-systematic approach with features of a scoping review. A semi-structured format was seen as most appropriate to report the current state of neurotechnology, associated recurring implications, and the 10-week timeframe of the report. This method was effective for understanding key developments and ranging trends from a multitude of sources, while not requiring an in-depth review of all existing studies relevant to neurotechnology usage, as would be the case in a systematic review. This method was also chosen given that the range of articles that were explored had different methodologies due to the different types of neurotechnologies and lacking standardized study methodologies.

A semi-systematic review was also helpful to identify relevant sources as close to the inclusion criteria as possible to provide a holistic overview of data on all aims of the project. Furthermore, as this review focuses on desk research rather than statistical or in-depth thematic analysis, a semi-systematic review was the most appropriate proposal for this project to identify relevant technologies and key associated themes.

The literature mapping approach included searching key terms across academic and non-academic databases. Sources were drawn from a multitude of disciplines, including but not limited to bioethics, law, social sciences, humanities, philosophy, and biomedicine. Searches were made on the following peer-reviewed journal platforms: PubMed, Google Scholar, JSTOR, Neuromodulation, and ScienceDirect. WIKISTIM[172], a resource on neuromodulation advances and published clinical research on neurotechnologies established in 2013, was also used to scope for studies by type of modulation. Legal, policy, and regulatory searches included search engines, the UK Public Access Registration Database (PARD), Westlaw, and Hansard.

Primary literature search terms

To address questions 1-3, the following search terms were used to identify primary literature sources.

(transcranial brain stimulation); ((transcranial magnetic stimulation) OR (repetitive transcranial magnetic stimulation)); ((transcranial direct current stimulation) OR (tDCS));

((transcranial alternating current stimulation) or (tACS)); ((deep brain stimulation) OR ((DBS) OR (pDBS) OR (aDBS))); ((brain-computer interfaces) OR (BCIs)); ((advanced therapeutic medicinal products) OR ((ATMPs)); (neural stem cell therapy); (((electrical stimulation) OR (ECT) OR (MCT) OR (TES) OR (CES)))); ((dorsal root ganglion stimulation) OR (DRG)); ((gastric electrical stimulation) OR (GES)); ((peripheral nerve stimulation) OR (PNS)); ((spinal cord stimulation) OR (SCS)); ((sacral nerve stimulation) OR (SNS)); ((motor cortex stimulation) OR (MCS)); ((dorsal spinal cord stimulation)); ((vagus nerve stimulation) OR (VNS)); ((Responsive Neurostimulation) OR (RNS)); ((((obsolescence) OR (replacement) OR (abandonment)) AND (neurotechnology))); ((((obsolescence) OR (replacement) OR (abandonment)) AND (implant)); (neurorights)

Analysis presented in the sections that answer questions 1-3 reference sources from the above results. For question 4, these sources, additional searches (including legal and policy instruments, reports, and statistics), and secondary academic sources were used to provide an in-depth analysis.

Inclusive criteria

1. Neurotechnologies within the taxonomy identified in the 2013 NCOB report that have been developed since publication AND are in active use in 2024;
2. 2. Neurotechnologies developed since 2013 that materially differ from the taxonomy identified in the 2013 NCOB report; and
3. 3. Neurotechnologies developed or in active use between 2013 and 2024 that are now obsolete.

The literature reviewed articles that focus on applications of neurotechnology as part of healthcare delivery or as ‘self-care’ for management of symptoms and/or diagnosable health conditions. There was also a focus on identifying areas specific to implications and usages of neurotechnologies for a paediatric population, questions over equity and social access, alongside questions over neurorights.

Exclusive criteria

All searches were limited to publications from 2013-2024, that specifically address neurotechnologies in active use throughout 2013-2024. Sources not written in English were excluded were from the primary literature search. Sources that do not have accessible full-text findings were excluded. Themes and sources focusing on neurotechnology for non-health related purposes, such as enhancement, were excluded.

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