

Neural Interface technologies: medical applications outside the body

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Strong clinical evidence is lacking, mechanisms are largely unknown and useful applications don't reach patients. Despite this, there is clear potential for therapeutic benefits for current, emerging and future applications.

Introduction

Neural interface technologies are used to treat a variety of medical conditions, mostly in the rehabilitation of people with neurological conditions such as stroke, but the quality of clinical evidence lags behind that for pharmacological therapies. Healthcare providers are rightly only willing to provide evidence-based, cost-effective therapies. Generating high-quality evidence for technologies used to treat complex conditions is challenging. There are often no agreed outcome measures and wide variations between individuals in terms of presentation and responsiveness. A single neural interface technology can often be used to treat different conditions and applied using different protocols. This makes the 'gold-standard' randomised controlled trial (RCT), where a treatment is compared to a placebo or standard treatment, an inadequate tool. Consequently, distinguishing between those technologies that are effective - or could be - and those that are not is a difficult task. The problem is further confounded by cost. While pharmaceutical companies are rich and have established research and development systems, neurological technology companies are mostly young and relatively poor. Because of this, emerging potentially useful neural interface technologies struggle to translate into clinical practice. To capitalise on the potentially hugely beneficial therapeutic field requires a reappraisal of how reliable evidence is gathered, impetus from funders and policy-makers and a global co-ordinated effort¹.

Neural interface technologies that are used outside the body have advantages over implanted systems in that they are: a) easy to apply; b) low risk; c) cheaper and therefore more likely to be used on a large scale; and d) less committing – ie they can be tried and easily abandoned if found not to be effective. They also have disadvantages over implanted systems in that they are: a) less likely to be accurately targeted; b) require more effort from the user in terms of donning and doffing and c) more likely to be incorrectly applied.

Classification of systems

Current and emerging applications can be classified into those that simply provide **stimulation** to the nervous system, either directly through the central nervous system (CNS) of the brain and spinal cord or to peripheral nerves, or targeting an area of the skin close to where a nerve enters a muscle – called the 'motor point'. Other systems use **recordings** from the nervous system, often in combination with recordings of movement, to provide information either to the patient or the clinician – i.e. providing insight into neural control mechanisms and behaviour. Other systems, and these tend to be emerging and future applications, **link the recordings to stimulation**, and are often termed 'closed-loop' systems. There is now a vast amount of research effort directed towards closed-loop brain computer interface (BCI) technologies, that

generate an intelligent response to a person's CNS or movement activity. Simple examples are using brain activity to control their prosthetic arm and hand - or using an electromyogram (EMG) or brain signal (EEG) to trigger electrical nerve stimulation. Finally, some systems take this intelligent feedback further in an aim to **change behaviour** using smart phone technologies.

Current Applications

Systems that use stimulation

The most common application is **functional electrical stimulation (FES)**, used in neuro-rehabilitation for the recovery of motor function. It can be subdivided into **orthotic** applications that result in an immediate improvement in motor performance and **therapeutic** applications that aim to improve motor performance over time. We must be cognisant of the fact that there is interaction between them, for example orthotic systems may have a therapeutic effect.

The most commonly used application is the 'drop-foot stimulator' (Figure 1). This is now recommended by both the National Institute for Health and Care Excellence (NICE)² and the Royal College of Physicians Clinical Guidelines for Stroke³, yet fewer than 10% of people who could benefit receive this treatment. The technology is simple. Electrical stimulation is applied through the skin to the nerves that activate the muscles that lift the foot during the swing-phase of walking. Timing of the stimulation is controlled by a pressure-sensitive switch worn in the shoe. Some systems use a movement sensor worn on the shin to detect when the leg is about to be swung forwards. The electrodes are usually applied through a cuff worn just below the knee (Figure 2). Implanted systems have been developed and tested and found to be as effective and preferred by patients⁴, but cost, translation and regulatory hurdles have inhibited their widespread use⁵.

FES is also commonly used (although more in the US than the UK) to treat pain. **Painful shoulder subluxation** is a common problem following stroke, caused by weakness of the muscles around the shoulder joint that maintain the position of the head of the humerus in the glenoid cavity, part of the shoulder blade. Stimulation is applied for long periods to re-align the shoulder joint, often switching between different muscles to avoid fatigue and a marked and long-term reduction in pain has been demonstrated⁶. It was originally hoped that the intervention might even lead to recovery of movement but evidence shows that this is not the case. **Transcutaneous electrical stimulation (TES)** that uses very low amplitude, pulsed stimulation is used for the treatment of chronic pain. The treatment is based on the 'gate control theory' (https://en.wikipedia.org/wiki/Gate_control_theory). If a nerve continuously fires over a long period of time an effect called habituation is observed, when the CNS ceases to respond to the stimulation. By stimulating sensory nerves at a sub-painful level, the sensory cortex, after a short period becomes less responsive to all sensory input, including painful stimuli. TES is often used for chronic back and joint pain as well as during childbirth.

Systems that use recordings

EMG recordings that monitor muscle activity for diagnostic purposes – for example to identify abnormal muscle activity, either weakness or spasticity – record electrical signals that are generated near the motor point where the motor nerve enters the muscle. Signals can be processed to detect muscle onset and offset times, together with the amplitude and frequency of firing. Frequency is particularly useful as it identifies when a muscle becomes fatigued. (High-frequency firing motor units ‘drop out’ when a muscle begins to fatigue, resulting in a fall in the median frequency). EMG is widely used to diagnose spasticity, where there is an increase in amplitude in response to a rapid stretch of the muscle, or to select injection sites when using Botulinum Toxin (BTX) to treat spastic muscles.

The challenge facing current NIT applications is that they are only available to a small percentage of patients who would benefit, partly because of cost, but also due to lack of education and awareness and hindered, especially in the UK, by a cumbersome funding mechanism.

Emerging Applications

Emerging applications are those for which there is proof of concept but which lack robust clinical evidence. Consequently, they tend only to be used by patients taking part in clinical trials. For technologies such as these, effort needs to be made to identify potentially useful applications, improve clinical evidence and accelerate translation into routine clinical practice. Some emerging applications have been commercialised and are being sold even though they lack robust clinical evidence. An example of this is the ‘Mollii Suit’, developed at the Karolinska Institute in Stockholm, Sweden, and marketed by Remotion.co.uk. Persuasive claims are made online (<http://www.remotion.co.uk>), but currently there is only one peer reviewed publication presenting clinical evidence⁷, along with a pilot RCT of 27 people with spasticity resulting from either stroke or cerebral palsy, and a NICE briefing Paper. (<https://www.nice.org.uk/advice/mib100>). The Mollii suit, which was CE marked in 2012, provides whole body low level electrical stimulation via electrodes embedded in the suit with the intention of reducing spasticity. There has been no research into the mechanism of effect, yet there is a growing weight of experiential evidence which has boosted sales, suggesting that factors other than robust clinical evidence drive translation of technologies into clinical practice^{5,8}. The company has been reported to have sales in excess of 1000 worldwide, mostly in the private sector.²⁰

Systems that use stimulation

There have been more than 200 animal and human trials of **transcranial magnetic stimulation (TMS)** and **transcranial direct current stimulation (tDCS)**, many reporting mechanistic changes within the CNS either recorded by functional magnetic resonance imaging (fMRI) or EMG responses to TMS, suggestive of increased cortical excitability⁹, which is known to be important in neuroplasticity and therefore recovery. Clinical benefits have also been reported but currently there is no Level 1 evidence from large RCTs. The problem is that there are many unknowns in terms of when and

how to apply it - and with whom. There is probably huge unrealised potential; however, systematic large-scale research is needed to understand the mechanisms of effect. Evidence is unlikely to be found through standard RCT methodology because of individual variability and the number of protocols that could be used. Similar challenges apply to paired associative stimulation (PAS), in which cortical stimulation (TMS) is timed with peripheral stimulation (FES) so that the train of impulses converge at the anterior horn cells (AHC) in the spinal cord at the same time. This not only increases immediate depolarisation of the AHC, generating a larger response, but also, via Hebbian learning, increases the potential for neuroplasticity and learning¹⁰. Clinical benefits of PAS have been shown in case studies¹¹ – but again without Level 1 evidence. tDCS and rTMS have also been used to treat clinical depression¹² but here too, there is poor understanding of mechanisms of action and although a large RCT funded by the National Institute for Health Research (NIHR), is currently being conducted (<https://ukctg.nihr.ac.uk/trials/trial-details/trial-details?trialId=14281>) there is currently a paucity of clinical evidence.

Implanted systems that stimulate the vagus nerve have been shown to be effective in treating clinical depression and more recently transcutaneous electrical nerve stimulation (TENS) – has also shown some benefits with far lower risk and cost¹⁹.

Advances are being made in materials science, electronics and signal processing that, among other benefits, could overcome the problems of muscle fatigue caused by repeated stimulation of the same motor points, enable accurate targeting of stimulation. For example, electrode arrays, created by 3D printing, could be integrated into clothing, facilitating stimulation that is more precise as well as being delivered using different combinations of sites to avoid the problem of fatigue. Combining that technology with iterative learning algorithms¹³ would provide an easy-to-use platform for triggering and controlling stimulation using intelligent feedback to show patients how they are performing and learning, so that recovery, would be accelerated..

Systems that use stimulation and recordings

Intelligent or closed-loop systems that apply stimulation in response to either a recorded signal, such as EMG or Electroencephalogram (EEG), or to an external event such as a movement sensor - so that it either coincides with a desire to move or the initiation of a movement - have greater potential, based on Hebbian learning, to promote neuroplasticity and this recovery. One of the simplest applications is FES cycling, where the position of the crank shaft triggers the stimulation of appropriate leg muscles. A recent study extended this to provide feedback based on the individual's voluntary effort as measured by the amount of torque on the pedals in a virtual reality cycle race. By providing feedback related to voluntary effort the individual was encouraged to work harder rather than allowing the electrical stimulation to do the work. A similar approach that used iterative learning control (ILC) has shown clinical benefits for stroke patients with loss of arm and hand function. ILC is used to adjust the level, timing and location of stimulation in response to performance, by comparing the desired trajectory of a movement with the actual trajectory so that only the minimum stimulation is provided to enable the patient to perform the movement

accurately. Stimulation is reduced on each iteration, until performance declines below a given threshold, at which point it is increased¹⁴.

Vibrotactile feedback, or sensory augmentation, is an emerging therapy that has improved balance in people with vestibular disorders¹⁵. Movements detected by electronic tilt sensors or postural sway detected by pressure sensors are linked to sensory stimulation, such as, for example, visual or auditory cues or a vibration on the tongue. Again, there is currently no strong clinical evidence, but the applications show promise.

We now need a better understanding of neuroplasticity, so that systems can be designed and used based on a deeper knowledge of learning. Neuroscience, greater understanding of motor learning principles and psychology can all also contribute to better application of NITs.

Systems that use recordings

EEG signals recorded from a simple, commercially available headset can be used to provide neural feedback. One application addresses central neuropathic pain (CNP), which is a common and debilitating problem following spinal cord injury and amputation. CNP is associated with changes in EEG signatures from the motor cortex, particularly a reduction in alpha wavebands and an increase in beta and theta wavebands. Change in EEG signatures towards normal patterns – with more alpha waves and fewer beta and theta ones - results in immediate relief of pain. There is some evidence that using neural feedback, in which patients play a computer game, which they win when they learn to change their EEG signatures towards normal, can result in both short and long-term reduction in pain.

Neural feedback is also used to motivate correct movement – for example providing a sensory stimulus to the skin to encourage a normal movement pattern. The simplest form of such feedback is to tell a patient when they are using compensatory movements -such as leaning forward rather than extending their arm when reaching to grasp an object. Recordings of movement, using inertial measurement units (IMUs), accelerometers, gyroscopes and magnetometers can be combined with recordings of muscle activity using mechanomyography (MMG), which employs a microphone type device that does not require electrical contact. These have been imbedded into a wearable garment (M-MARK) and demonstrated to provide motivating feedback to patients recovering arm and hand function following stroke¹⁶. This has also been shown to provide valid and reliable information for clinicians at an impairment level, in terms of abnormal movement and muscle activity. Such systems hold great promise, not just for therapy, but also for understanding the causes of loss of function and mechanisms of recovery. A spin-off from M-MARK has been developed to be worn if and when astronauts eventually undertake a manned space mission to Mars to enable them to monitor changes in muscle strength and endurance while in space. Wearable sensor technology is a rich field of research that holds the key to intelligent control of stimulation.

Wearable magnetoencephalography (MEG) is a technology that could overcome current limitations in observing and imaging brain activity during functional activities

because the patient needs to be still and inside a large scanner. A wearable MEG system has been developed that incorporates quantum sensors, which do not require superconducting technology, and a new technique for cancelling ambient magnetic fields. Comprising a lightweight helmet that allows head movement, the new system supports measurement of MEG data at millisecond resolution during movement including head nodding and ball play¹⁷. The system opens up new possibilities for MEG scanning to enable a better understanding of brain activity during movement.

Behavioural Change Applications

Apps may be developed to maintain fitness into old age and reduce complications of Type 2 diabetes, obesity, heart disease and the risk of stroke, as well as increasing physical activity post-stroke

Technologies that detect muscle fatigue and strength during exercise can contribute to general well-being and sport to optimise training. When a muscle becomes fatigued, the median frequency falls as the fast fatiguing fibres 'drop out'. It is not beneficial to continue to work a fatigued muscle but important to work up to the fatigue point. MMGs can detect changes in median frequency that enable this point to be identified accurately.

Future Applications

Future applications are those for which there is currently no clinical evidence in humans. They are more about ideas of what is possible than tangible technologies. Neural interface technology is not a pure science, and therefore, it is dependent for its growth on advances in other fields, such as materials science, electronics, micro-chip technology, signal processing, neuroscience and psychology. Advances in nanotechnology are likely to have a big influence on outside the body applications. Future applications will be those that capitalise on miniaturisation of hardware and artificial intelligence. One example is that of very small sensors that can be attached to the skin like adhesive bandage plasters to monitor movement and muscle activity (<https://www.smithsonianmag.com/innovation/flexible-sensors-could-help-monitor-stroke-patient-in-recovery-180968322/>). Such sensors have the advantage of being convenient and therefore able to collect data over long periods, mapping behaviour and providing feedback. Currently their reliability has not been proven and claims are yet to be supported by evidence. Some future applications pose ethical concerns, for example cortical stimulation to change behaviour. The following are some examples of what might be possible.

Closed loop systems that use algorithms to respond to performance are already emerging, for example ILC, described above. However much more benefit may arise if the algorithms can learn from behavioural responses. The simplest form might be a system for motor training that sets new targets or tasks to the patient in response to previous performance, in much the same way that a therapist might, but also identifies how each patient learns best. Some people respond best when they are achieving a 90% success rate, others considerably less. Work published by Matarić and Winstein¹⁸ identified different character types – such as people who respond well to gentle

encouragement and others to a more aggressive approach. The challenge of such a system is to classify behavioural types and apply responses appropriately.

Systems might be developed that detect why movement is impaired and respond appropriately, for example: decreased performance due to muscle fatigue requiring rest; or decreased performance due to spasticity in antagonist muscle groups requiring stretching or a higher level of stimulation.

People who might use assistive technology for long term support rather than recovery could benefit from the ability of a system to use EEG signals from the motor cortex to detect the desire to perform a movement and communicate it using a system similar to a digital voice assistant but without the need for speech. This could be linked either to an electrical stimulator or to a robot, which would not only increase personal independence but also be cost-effective if it reduced the amount of personal care required.

Non-invasive functional imaging could be used for diagnostics, for example in sleep studies or anesthesia, using technologies like electroencephalography (EEG), functional near-infrared spectroscopy (fNIRS), functional magnetic resonance imaging (fMRI) or wearable magnetoencephalography (MEG)

Behavioural Change Applications

'Telehealth' applications could provide connectivity between patients at home and clinicians in a hospital. Sensor data transmitted via the internet could be used by health professionals to monitor health and activity. Similar data such as muscle activity, used as feedback to patients, has the potential to encourage positive behaviours and, if shared with others, could be translated into a competitive game.

Summary

Potential for medical outside-the-body application of neural interface technologies is vast and this chapter has only scraped the surface. Some technologies that have demonstrated clinical benefits have made it as far as patients, even though only a small fraction of those who would benefit are currently able to access them. The great challenges now are: firstly, to understand the mechanisms through which they work to inform future developments and improve our understanding of the brain; and secondly, to identify which emerging technologies are useful, then translate them rapidly into clinical practice. Future applications may have even more power to change lives; as a society we must invest in research that will accelerate the process of understanding and translating them so that they can be used to improve lives and reduce health service costs.

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