25 YEARS OF TRANSCRANIAL MAGNETIC STIMULATION – where are we now? Where are we going?

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Electricity is the language of the brain: neurons communicate with one another via electric impulses known as action potentials, which constitute the basic unit of information processing in the central nervous system. A key goal in neuroscience research and clinical application is to manipulate this electrical brain activity.

Early pioneers in neurosurgery applied microelectrodes to the surface of brain to determine the functional role of specific areas. By constructing a functional map on the brain surface, surgeons can then minimise, as much as possible, post-operative loss of function. Patients, who remain conscious during this type of surgery, describe the effect of stimulation, including the evocation of old memories, smells or associations. These vivid first-hand accounts provide fascinating insights into the workings of this remarkable mass of grey matter; however, by necessity, such invasive procedures are limited in scope.

Ultimately, the goal is to stimulate the brain non-invasively, by somehow crossing the barrier of the cranium. So-called *transcranial* stimulation was first achieved with currents applied directly to the scalp(1). However, because of the relatively high electrical resistance of the skull, a large current must be applied to the scalp in order to deliver enough current to activate underlying brain cells. Therefore, although strictly non-invasive, transcranial electric stimulation (TES) is in practice too painful for general use.

The breakthrough in non-invasive brain stimulation came in 1985, when Barker and colleagues at Sheffield University published a seminal paper in the Lancet describing a painless procedure for human transcranial stimulation(2). In this brief, but landmark scientific report, they described how they could use magnetic fields to generate local electric currents in the brain. This novel approach, now known as transcranial magnetic stimulation (TMS), exploits the principles of electromagnetic induction. During TMS, an insulated coil is placed against the scalp surface overlying the targeted brain area. When discharged, the coil generates a brief magnetic pulse that passes unimpeded through the skull and into the brain. This time-varying magnetic field in turn generates a secondary current within the underlying brain region.

Barker and colleagues originally developed TMS as a clinical diagnostic tool for assessing the integrity of nerve pathways following damage caused by disease, stroke or spinal cord injuries. In subsequent years, applications for treatment have also been explored. Early enthusiasm for the therapeutic use of TMS focused on psychiatric conditions, particularly depression. Although modest improvements have been observed, there remain methodological issues associated with identifying the therapeutic mechanism. Therapeutic applications have also been explored for a range of other psychiatric conditions, with some promising results; however, more research is needed to establish the clinical relevance of TMS in psychiatry(3).

As a research tool, the success of TMS is unqualified. Even today, 25 years on, TMS is the only available method to activate specific brain areas. Most commonly, TMS is used to probe the functional role of a given brain area by introducing a sudden burst of activity that effectively disrupts normal function. As a tool for brain disruption, TMS complements measurement techniques such as functional magnetic resonance imaging. Where brain imaging can identify which brain areas are more or less active under specific conditions, TMS can be used to test whether the observed activity directly contributes to the function of interest.

What does the future hold for brain stimulation? One of the most important limitations for TMS is depth. Currently, TMS can only be used to stimulate relatively superficial brain areas. A non-invasive method for stimulating deep brain structures would have a profound impact in both research and clinical settings. One potentially exciting lead comes from ultrasound. Recently, researchers have provided proof-of-principle evidence that high-frequency sound waves emitted outside the head can generate focal activity in deep brain structures without damaging neural tissue(4). Nevertheless, it may be many years before ultrasound stimulation will be approved for human use.

Since Barker's landmark demonstration of painless, non-invasive brain stimulation, TMS has become a standard tool for neuroscientific research, clinical diagnoses, and increasingly, therapy. Local industry has also capitalised on this UK innovation. For example, The Magstim Company Limited, based in Whitland, is now a world-leading manufacturer, and distributor of TMS, and was recently awarded the Queen's Award for Enterprise, in recognition of their expanding worldwide operations. This company continues to work closely with the development team at Sheffield, as well as other UK research centres, demonstrating how fundamental research and innovation can directly benefit UK industry, and economic competitiveness.

1 Merton PA, Hill DK, Morton HB, & Marsden CD (1982) Scope of a technique for electrical stimulation of human brain, spinal cord, and muscle. (Translated from eng) *Lancet* 2(8298):597-600 (in eng).
2 Barker AT, Jalinous R, & Freeston IL (1985) Non-invasive magnetic stimulation of human motor cortex. (Translated from eng) *Lancet* 1(8437):1106-1107 (in eng).
3 Ridding MC & Rothwell JC (2007) Is there a future for therapeutic use of transcranial magnetic stimulation? (Translated from eng) *Nat Rev Neurosci* 8(7):559-567 (in eng).
4 Tufail Y, et al. (2010) Transcranial pulsed ultrasound stimulates intact brain circuits. (Translated from eng) *Neuron* 66(5):681-694 (in eng).