Focusing attention on transcranial magnetic stimulation

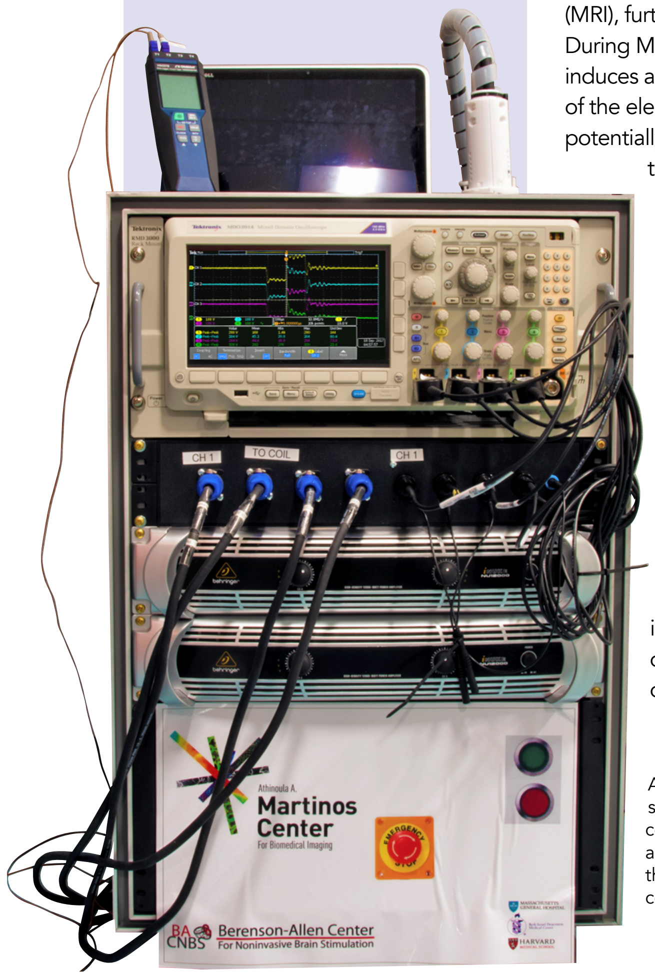
Dr Giorgio Bonmassar, Associate Professor of Radiology at Harvard Medical School, has developed a method of magnetically stimulating excitable tissues, such as those in the heart and brain, which overcomes many of the limitations of both direct electrical stimulation and transcranial magnetic stimulation.

The therapeutic and research benefits of electrically stimulating tissues are long established, from pacemakers and treatments for movement disorders such as Parkinson's disease to the identification of causal relationships between brain regions and functional responses. Initially, these were limited to direct electrical stimulation, by inserting fine electrodes into heart or brain tissue and delivering an appropriate current.

This approach is clearly not without its problems. Electrode implantation itself poses risks to the individual, and with the advent of magnetic resonance imaging (MRI), further complications were created. During MRI scanning, the 'antenna effect' induces an electrical current in the tip of the electrode which dissipates as heat; potentially causing irreversible damage to the tissue surrounding it.

DONE WITH MAGNETS

Transcranial magnetic stimulation (TMS) offered the potential to overcome these issues by firstly not requiring invasive surgical procedures. Stimulation is effected by placing a magnetic coil in close proximity to the target area of the brain; varying the magnetic field causes an electric current to flow in a small area of the brain through electromagnetic induction. It has been useful diagnostically in a range of diseases which relate to the motor cortex, such as stroke, multiple sclerosis, and motor neuron diseases, it has also been used to treat neuropathic pain (pain caused by damage or disease affecting the region of the brain which deals with bodily sensations).



An image of the complete µTMS system. The µTMS system is composed of safety monitors (scope and thermometer), class D-amplifiers, the computer and the stimulator that contains the µTMS coil and aerogel.

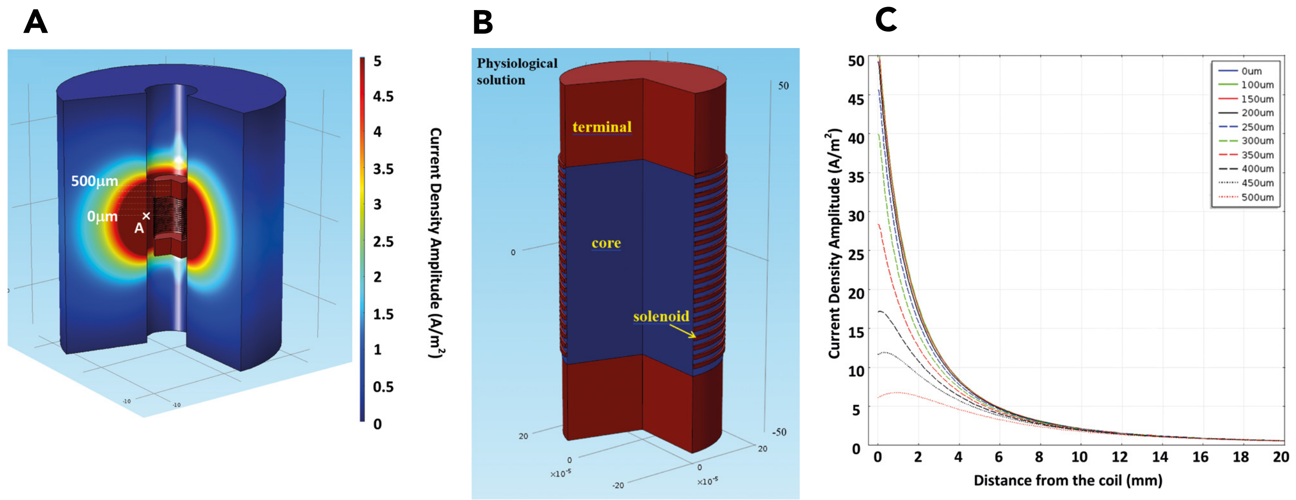
One other advantage of TMS is that it can be used in conjunction with functional MRI to improve our understanding on how TMS stimulates the brain, and its probes can be built into special MRI-safe headsets and stimulation delivered during scanning. The major disadvantage is its spatial resolution, fine targeting of the stimulation is difficult due to the properties of magnetic fields and the engineering limits of electromagnetic coil design.

AN IMPRECISE SCIENCE

'Bleed over' into nearby areas of the brain mean that its use as a research tool is limited. However, it has been successfully deployed to interrogate motor pathways, language organisation and for pre-surgical evaluation of patients. Its use as a mapping tool to assess how neural pathways are disrupted in brain tumour development, cerebral palsy and epilepsy are perhaps the most clinically relevant uses of this technology, providing vital information to physicians on the progress of these diseases.

The therapeutic uses of both TMS and direct electrical stimulation are now beginning to overlap, the networked nature of the brain means that there are nodes in the network which have the capacity to impact multiple disease expressions. These can be stimulated either directly, as is more usual for deep tissue stimulation, or by TMS which is able to operate only at relatively shallow regions due to the method of delivery.

Results of electromagnetic simulations. (A) 3D Current density distributions in a µMS coil, (B) geometry used in the electromagnetic simulations and (C) current density along the x or y-axis at distances shown in (A) from the centre of a 400µm diameter µMS coil.



FINER FOCUS

Dr Bonmassar's response to this situation was to develop what might be considered a hybrid of the two methods, implantable micro magnetic stimulators (µMS) which are able to deliver focused stimulation to specific areas of the brain. As these stimulators are electrically isolated from the tissue, instead of delivering their stimulation via magnetic fields, they can be made MRI-safe and prevent the heat damage associated with traditional implantable electrodes. This one step removed property of magnetic stimulation also has the advantage of allowing the coils to be encased in bio-compatible materials, reducing inflammation at the site of implantation.

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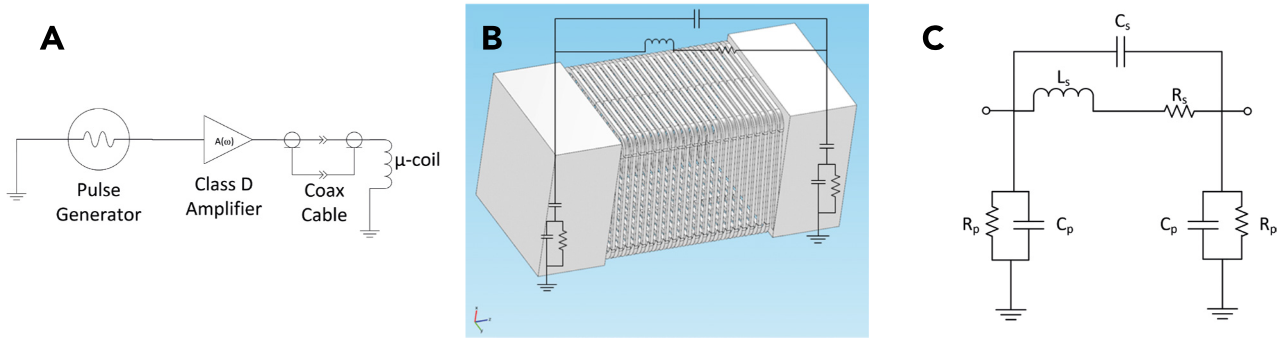
In order to assess if this concept would be viable as a means of neuronal stimulation, Dr Bonmassar and his team tested the prototypes on isolated neuronal cells. Using explanted retinal tissue from rabbits, they first measured its response to flashes of light to ensure the ganglia (a cluster of nerve cells) were active. They then lined up their µMS coils and proceeded to stimulate the same nerves by generating a time-varying magnetic field.

SEEING THE LIGHT

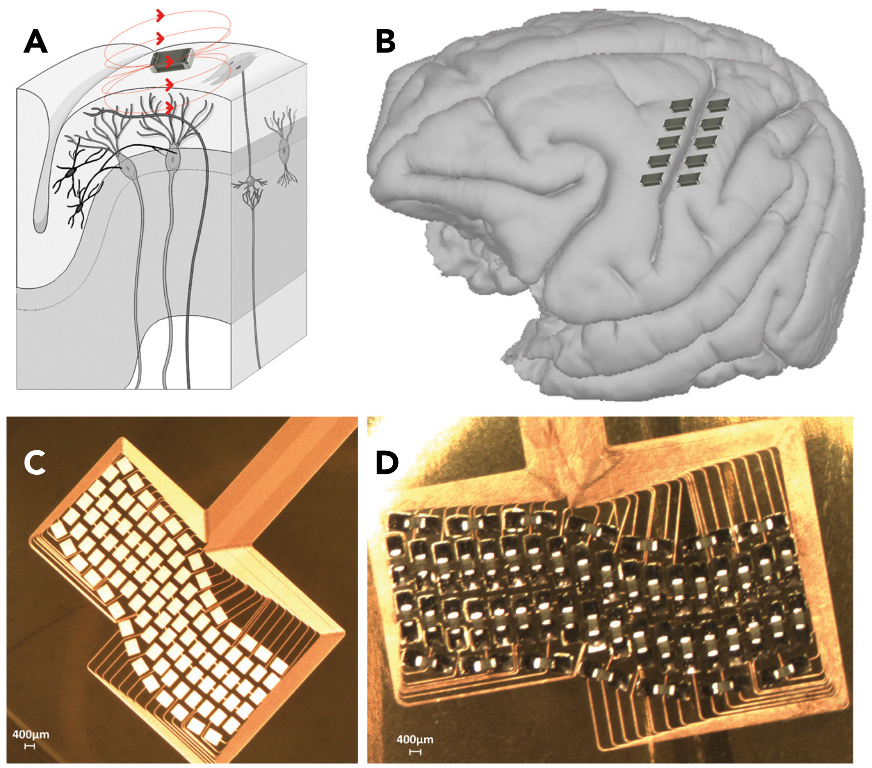
All the cells which responded to light stimulation also responded to µMS. Dr Bonmassar described the results in the journal *Nature* as, "The amplitude and kinetics of individual biphasic waveforms [where the response cycles above and below the baseline value] were nearly identical to that of action potentials elicited in response to light stimuli, strongly suggesting that the biphasic waveforms were in fact action potentials [the wave of electrical energy that underlies a nerve impulse]." These exciting results laid the foundations for further refinement of the process *in vitro* and demonstrated the real potential of the product he had designed.

The team continued to investigate the mechanism and salient features of the stimulation effects; showing that the orientation of the coil and the magnitude of the initiating current, amongst other parameters, were fundamental to the response obtained. This result demonstrates a level of specificity and tuning which could prove vital for both the clinical and research applications of the technology.

Dr Bonmassar designed the experiments carefully. "Potential contributions from



In both the µMS and µTMS systems, the coils were driven by a class D amplifier (A). An N-turn µMS coil (B) was studied using an equivalent electrical circuit (C), which takes into account different sources of electric and magnetic losses. Magnetic flux losses that do not contribute to Joule heating constitute those contributing to microscopic magnetic stimulation of the excitable tissue. Thus, µMS optimisation requires a low Q-factor design.



Cortical stimulation by μMS. (A) the magnetic field induced by the μMS coil can excite cortical tissue when neuron axons are oriented perpendicular to the coil axis, and proper distance and pulse shapes are used, (B) design of a μMS coils grid that follows the curvature of the somatomotor cortex of a nonhuman primate. (C) The layout of the actual FLEX circuit built with 64 gold traces with 25μm width deposited with gold sputtering on 50μm thick polyamide substrate and (D) the FLEX populated with 60 μMS coils.

several non-magnetic factors including leaking electrical current, heating of tissue, and mechanical vibration were all eliminated," he said, "allowing us to conclude that small magnetic fields can elicit action potentials." He goes on to describe the effect this will have on the spatial resolution of magnetic stimulation as akin to the leap from low-field MRI technology to the ultra-high field MRI (currently not extensively deployed for clinical use).

SAME BENEFITS, SMALLER PACKAGE

The key to achieving this is adapting the μMS technology to create the first generation of miniaturised TMS probes (μTMS) allowing for ultra-focal non-invasive brain stimulation. Advances in micro-fabrication allow for long electromagnetic coils to be created in rings as small as a few millimetres across. The length of the coil is vital to producing a field with sufficient strength to penetrate the skull while maintaining a low resistance ensures that heat generation remains low enough to prevent scalp discomfort.

The next step for Dr Bonmassar and his team of collaborators and researchers is to move to first-in-human trials of the technology. This research will demonstrate μTMS safety and reliability for clinical use as well as give them the opportunity to compare its mapping abilities to currently approved TMS systems. Dr Bonmassar believes that these early tests will clearly demonstrate the superior spatial precision and resolution of μTMS over traditional systems.

In the process of this research, they will further refine and develop coil design and production to optimise the reliability of the technology. The aim is to manufacture class-leading stimulators consisting of two-coil arrays, opening up new possibilities in the exploration of cortico-cortical interaction. These arrays will distinguish activation of the somatosensory cortex over the motor cortex, a technique which is not possible with even state of the art current TMS technology.

FOCUS ON THE FUTURE

The team already have extensive modelling results to direct coil design, indicating that the μTMS coils produce a substantially more focused stimulation than traditional TMS probes while using a much smaller current. Dr Bonmassar believes this is due to micro coils being capable of eliciting action potentials at lower field thresholds due to the higher spatial gradient (their small size means a sharper decline in signal with distance).

"Micro-magnetic stimulation is an emerging technology with great promise to revolutionise therapeutic stimulation of the human nervous system," says Dr Bonmassar, "Our project is adapting this novel technology to develop the first generation of μTMS probes." He is confident that as they push this technology forward, "it will enable for the first time, ultra-high resolution non-invasive stimulation of the human brain with applications across therapeutic and exploratory neuroscience."

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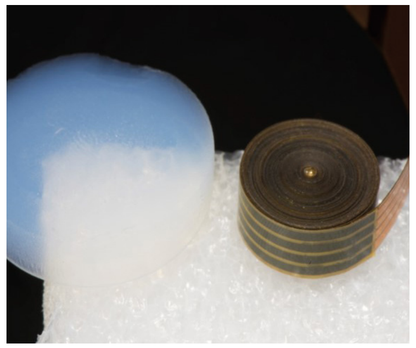

Above: The μTMS coil and an aerogel disk. Excess skin heating despite large currents and power demands was greatly reduced by inserting a 2-mm layer of aerogel between the skin and μTMS coils. Simulations and measurements show that heating transfer to skin was minimised using aerogel thermal superinsulation. Aerogel is an advanced material cited in the "Guinness Book of Records" (15 entries) for its unique best thermal insulation property.

Behind the Research

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Research Objectives

Project Narrative Micro-magnetic stimulation (μMS) is an emerging technology with a great promise to revolutionise therapeutic stimulation of human nervous system. In this project, they will adapt this novel technology to develop the first generation of miniaturised transcranial magnetic stimulation (μTMS) probes. The outcome will enable for the first time, ultra-high resolution non- invasive stimulation of the human brain with applications in therapeutic and exploratory neuroscience.

Detail

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Bio

Giorgio Bonmassar, PhD is an Associate Professor of Radiology at Massachusetts General Hospital and Harvard Medical School with expertise of over twenty years in electrophysiology systems measurements simultaneous to MRI, including a set of microelectrodes that are truly MRI-invisible that led to a Science article. The feasibility of Micro-magnetic stimulation (μMS) implanted in deep brain structures was first shown by his group of being capable of delivering therapeutic stimulation with effects analogous to the state-of-the-art deep brain stimulation.

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Personal Response

How will this technology impact clinical neurobiology therapy and research?

" In clinical practice, cortical mapping of language, as well as the systematic exploration of the motor cortical outputs can be beneficial for the pre-surgical evaluation of patients in order to characterise eloquent cortex whilst reducing the need for intraoperative evaluation. In addition to the highly improved focality, which allows for precise selection of a stimulation site, the focal simulation also reduces extraneous activation of non-targeted brain areas. Furthermore, the significantly reduced size of μTMS elements allows integrating them into multi-channel conformal head arrays for simultaneous multi-focal stimulation (e.g., a TMS helmet will be finally feasible). In the realm of network stimulation, the ability to apply TMS simultaneously in multiple sites to inhibit certain nodes while facilitating others will introduce a significant leap in the study of altered brain networks in psychiatric and neurological disorders. "