

This response was submitted to an expert consultation held by the Nuffield Council on Bioethics on *Novel neurotechnologies: intervening in the brain* in February 2012. The views expressed are solely those of the respondent(s) and not those of the Council.

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1. Please briefly describe the neurotechnology or neurotechnologies you are working with and the nature of your research. Please also describe whether you do basic/translational/clinical research.

I use Transcranial Magnetic Stimulation (TMS) as a mean to interact with ongoing brain oscillatory activity (as measured via electroencephalography) and ultimately to manipulate behaviour in desired directions. I aim at understanding the functional role of brain oscillations in perception, cognition and action by manipulating them, e.g. through their entrainment via rhythmic TMS protocols. TMS is applied in a rhythmic mode at a frequency mimicking that of the brain thought to be of importance for a certain function (e.g. visual perception, attention, action, etc). The research I perform is mainly basic research with a potential to become translational and applied to clinical settings.

2. What, if any, are currently the main clinical applications of this technology?

TMS in itself is a relatively young technique and the approach I developed with other colleagues is at its initial stage with increasing reports over the last 3-4 years by few groups. Although one of the aims is certainly to develop clinical protocols, it still represent a very early stage of experimentation and several years of active basic research are needed to implement translational/clinical research. Broadly speaking, over the last 10-15 years, TMS has been tested in its repetitive mode to treat depression, with promising outcome including reduced symptoms.

3. What clinical applications of the technology do you envisage *in the future*? (Please try to specify a timeframe for these developments)

Manipulating brain oscillations could be of advantage in those situations where alterations in oscillatory activity have been found (e.g. parkinsons disease, stroke patients, epilepsy etc). Applications of this technique might help in the future to restore functions and/or relief from symptoms. However significant basic research is necessary to understand the mechanism of action of this technique on the normal brain and to envisage any potential implementation in clinical populations. Scientific progresses are generally slow in this sense and we might expect to see some development in this direction in no less than 5-10 years.

4. What are, or were, the main barriers to overcome in translating your research into the clinical application(s)?

As already mentioned, the main barrier is its very early development stage which requires further investigation before any protocol could be sensibly translated or applied to a clinical population.

5. How could the technology you work with help address unmet needs of neurologists and psychiatrists?

In the future, the use of this technology might serve as a potential therapeutic tool in a series of diseases.

Clinical trials could be implemented both in psychiatric (see e.g. depression) and neurological populations (see e.g. epilepsy) with the idea of manipulating brain oscillations in desired direction and implement brain plasticity thereafter.

6. What do the technologies currently cost, and will it be possible to include them as part of regular service in the NHS? If not, what are the likely markets or funders?

I do not have recent figures of TMS machine cost at hand.  
This technology can be run by trained and specialized personnel, in accordance with safety guidelines (see Rossi et al., 2009 Clin Neurophysiol). In principle, it might be considered as part of regular service in specialized NHS centres.

7. Are there currently any non-medical applications of this technology? How far have these been researched and developed and commercialised? Are devices you work with available on the internet/direct-to-consumer?

No that I'm aware of. However alternative to magnetic stimulation, electric stimulation devices have been developed. Although based on a different mechanism, the application of a weak current over the scalp has been shown to act as a potential modulator of brain excitability and oscillatory activity.

8. What non-medical applications of the technology do you envisage *in the future*? (Please try to specify a timeframe for these developments)

Electrical stimulation devices known as Transcranial direct current (tDCS) or alternate current (tACS) stimulators might be developed in the future for non medical applications, e.g. this might involve modulation of memory functions (see Marshall et al., 2006 Nature).

9. Are there any unexpected or unintended effects of the technology, and if so, how frequent and serious are they? (Where applicable, please include clinical and non-medical applications)

One of the main (although extremely infrequent) and most serious side effects of the use of TMS is the possibility to induce an isolated seizure episode during the stimulation session. However the chances that this can happen are less than 1% in the tested population. This percentage is narrowed down to virtually 0% when safety guidelines are strictly followed. For an exhaustive review see Rossi et al., Clin Neurophysiol 2009.  
Other infrequent undesired side effects are momentary headaches, which can be normally treated with paracetamol.  
Finally, given the high pitch of the sound that comes along with each TMS pulse, infrequent and momentary ear noise can be induced, but those can be easily avoided if earplugs are used during the stimulation session.

10. Is there anything in your area of research and development that you find particularly problematic? Where do you feel you need more guidance? What is there in the way of guidance for these problems already?

### Questions if you work with patients

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11. In your experience, what do patients and/or users expect from the technology?

12. What risks are patients and/or users willing to take, and why?

13. How well-informed are patients and/or users about the technology, and how helpful is the notion of informed consent in your experience? What happens if patients lack the capacity to consent?

14. After an intervention: are expectations of patients and/or users regularly met?

### Broader questions about the field of novel neurotechnologies

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15. If you consider the whole field of novel neurotechnology development, what advances do you believe are possible over the next ten years? What aspects (e.g. material technologies, theories of underlying mechanisms and pathways, treatment targets) of today's novel neurotechnologies will be with us in ten years' time?

The advent of novel neurotechnologies brought an exponential growth in general knowledge, with the

possibility to more directly and 'causally' test theories of underlying mechanisms and pathways, explore new ways of assessing hypotheses and generally speeding up the all process of scientific knowledge. Following this logic, all the aspects of novel technologies that contribute to new ways to explore the problems at hand with an added value to knowledge will make part of our new consolidated body of technologies. Among those, testing brain-behaviour causality becomes the important advance that comes along the development of novel neurothechnologies.

16. Looking at the whole field, what are the main challenges/barriers in the innovation trajectory from idea to bedside/ market for novel neurotechnologies, and how could these be tackled?

Main barriers are represented by the physics and biological interface constraints that each technology is built up with. With this in mind, a multidimensional approach to innovation might open new ventures for exploring ways of thinking novel neurotechnologies in the years to come.

17. Recently concerns have been raised about the regulatory regime for medical devices both in the US and in Europe. What are your views on the current regulatory regime for novel neurotechnologies in your region, and in what ways, if at all, do you think it needs to be improved?

18. Could there be a need for more regulation of novel neurotechnologies *in the future*; and if so, what should this permit, prevent, and inspire?

Neurotechnologies should be always run by specialized or supervised personnel. They should be trained according to the functions and applications of the new neurotechnology. Crucially, safety guidelines should represent one of the main pillars of their specialization, directing their daily practice. Where safety guidelines are yet not provided, caution with the use of parameters should be taken at all times.

19. Advances in neurotechnologies raise a lot of interest and many hopes. Do you believe that there is 'hype' surrounding these technologies? If so, how can we distinguish between the 'hype' and the reality? And who is responsible for creating the hope and for managing the hype?

As for any other field of knowledge where new proposals and hopes are proposed/explored, the risk for 'hype' is subtle and we all should be aware of how to distinguish between genuine and scientifically supported hope for real progress vs. 'hype'. Scientific communication processes (i.e. peer review, publication, scientific replication) should be responsible for controlling the goodness of the scientific advances. Nevertheless, sensationalism can easily bypass the scientific communication route with spreading of erroneous or misleading information into media and common channels of information (newspaper, internet etc).

A general comment on how to overcome this problem is to create awareness in the companies providing scientific and general public information about possible pitfalls in the scientific communication process,

and always refer to the source of the communication.

As a post-hoc process, re-establish the proper scientific communication route where erroneous or misleading information has been disseminated.

20. What do you think are the main social and ethical concerns raised by novel neurotechnologies and their applications?

As novel neurothechnologies, their long term impact, mechanism of action and possible side effects need to be monitored.

21. Who do you think should be the target audience for a report on the ethics of novel neurotechnologies that intervene in the brain? If the Working Party developed direct recommendations to any particular groups or institutions, who should they be in your view? What would you like the Working Party to recommend?