BRAIN STIMULATION
Training programs

TMS for Depression Online Course
Frequently Asked Questions

Q&A Session 1

Is TMS dangerous if targeted incorrectly?

In brief, the evidence we have is that TMS seems to be remarkably safe even when it is not being used in a therapeutic context. There have been an enormous range of research studies done in healthy control individuals and none of these have shown any persistent deficits or the like. I suspect that there is a strong homeostatic push back against any changes in brain function if there isn't an underlying problem to begin with. Having said this, we are very careful around targeting as we want to maximise the likelihood of benefit and not take any risks, but TMS generally seems to be an extremely safe procedure.

What is involved in the placement of right sided DLPFC?

Localization of treatment on the right just mimics what is done on the left. You can use the beam F3 or 5-6cm approaches and just adapt to the other side.

How do you approach off-label applications?

Use of all TMS to treat conditions that are not listed on the device indication on the Australian register for therapeutic goods (ARTG) is typically considered off label. Providing treatment for off label conditions should be done under the auspices of a clinical trial or potentially using the Special Access Scheme (SAS) scheme for approval of off label treatments. There should be a process within an organisation for the institutional approval of the TMS application that is being considered, whether this is on or off label.

Patient Status and assessment of RMT

A number of factors can alter cortical excitability and should be taken into account when assessing the RMT and then determining the intensive treatment. Ideally, the patient will be in a similar physiological state when they have their RMT done as when they are receiving treatment. We do know that things like sleep deprivation can affect cortical excitability and this can certainly be modified by medication. If there are significant changes in the patient status between when they had their RMT measured and when they present for a new treatment, it would be sensible to treat at a somewhat lower intensity for the current treatment session or reassess the RMT intensity before treatment if possible.

Different methods for RMT assessment

We have provided an outline of one method for RMT assessment in the course but this is not the only way in which it can be done appropriately. For example, there are adaptive algorithms for devices that determine the RMT based upon a series of pulses of varying intensity. Some of these algorithms have been systematically evaluated and validated. Coil manufacturers also have some variations in the methods of actually localizing the coil based on their specific hardware.

Alternative treatment site such as the DMPFC

Studies have explored the DMPFC and the orbitofrontal cortex as potential treatment targets. However, there are no substantive sham controlled clinical trial or equivalence / noninferiority trials have indicated that these targets are as effective as standard treatment approaches. As such, they still should be considered somewhat experimental. It is my view that treatment at these sites should only be done as part of research or under special circumstances and where a patient is clearly informed of the non-standard nature of the treatment they are receiving.

Use of multiple TBS sessions in a day

The use of intensive/accelerated TMS or TBS protocols has gathered a lot of attention in recent years. However, these approaches are still very new and have not been evaluated in large non-inferiority or sham -controlled trials. At this stage I think they are still experimental and should be used in clinical trials or only under special circumstances where patients provide explicit informed consent as to the non-standard nature of the treatment they are receiving.

Q&A Session 2

TMS PROTOCOLS

- **In rTMS for depression do you use the "FDA protocol" of 10 Hz, 4 seconds train duration, 26 second interval, 3000 pulses over 37.5 minutes? Or are you moving to a shorter high frequency treatment or even iTBS treatment?**

Do we still use the standard FDA approved protocol and where does that fit into the different ways we can go about offering TMS eg TBS, shorter protocols?

In the US, Neuronetics, a TMS device manufacturer, had a specific protocol approved with a significantly shorter inter-train interval (the 'DASH protocol' – 11 secs – bringing the overall treatment time to approx. 19 mins rather than approx. 37minutes. This was approved by the FDA with pre-clinical data suggesting it was just as safe as the standard protocol. They have since published some real world follow up data comparing this shorter protocol with the standard one, indicating similar response and remission rates.

The issue with protocols like this is that there is an enormous body of research showing the efficacy of a relatively standard way of providing treatment, 10Hz stimulation, 4sec trains, and a relatively long, 25 second inter-train interval. There is less evidence supporting the variations in these protocols e.g. those with shorter ITI: the protocol approved by the FDA was not supported by a large efficacy study or smaller non-inferiority study. However, the likelihood of significant differences in

clinical response with these variations, including shorter intervals, is small, with no safety issues identified.

We have also done a lot of treatments and studies with shorter ITI eg 15 seconds – and have not identified any significant safety concerns.

Therefore, I don't see issues with providing treatment over this slightly shorter time.

TBS PROTOCOLS

TBS is slightly more complicated. A significant non-inferiority study of 400 patients in Canada showed non-inferiority to standard treatment TMS. This has been used as evidence for use for clinical practice. TBS is used in many contexts internationally and increasingly locally and was also approved for clinical use in the US by the FDA based on this non-inferiority study.

TBS can create some issues in clinical practice with some machines. When giving TBS at high intensities (ie anything above 50% of the machine's intensity) there can be a 'roll off' effect, an intensity drop off, meaning particularly for patients with high thresholds, you may not be providing the treatment at the full dose you think you are providing. This is a complex issue, you need to be aware if this is an issue with your machine and discuss with device provider, educate yourself about it and establish limitations of the machine you are using.

- **Is there still not enough evidence for iTBS in treating depression? Recent researches regarding iTBS in treating depression have used iTBS 1800 pulses frequently with fair response.**
- **There has been few researches focusing on the role of cTBS in the treatment of depression or anxiety disorders. What's your opinion?**
- **Do you think iTBS 1800 pulses on L-DLPFC is more effective than traditional HF-rTMS? If a depressive patient fail to respond to HF-LDLPFC and sequential bilateral rTMS, do you think it is worth a try for iTBS 1800 pulses?**

    - If you look at pre-clinical data, if you extend the duration of a TBS train beyond the standard length, you actually get a lesser effect, and occasionally reversal of effects compared to the standard stimulation train lengths. These are preclinical studies, usually using a single session, often applied to the motor cortex in healthy controls, and there are significant issues with translating these findings into clinical practice.
    - Currently, anything other than the standard 3 min intermittent TBS depression protocol is experimental, and I don't think should be used routinely in clinical practice. The 3 min iTBS protocol is the protocol that was in the non-inferiority study demonstrating similar efficacy to standard treatment. Longer protocols have been investigated, but only in small studies so far.
    - Continuous TBS to right DLPFC is still experimental at this stage, data is limited

What is your opinion about SAINT protocol in Stanford University? Is it appropriate to deliver brain stimulation 5 times per day ?

- Stanford SAINT (now SNT) protocol is a form of accelerated TMS. It involves neuro-navigation targeting of treatment site, long stimulation trains of iTBS, high intensity, high dose (5 treatments a day). High remission rates, high resolution of suicidal ideation reported in open label studies. First double-blind data very positive, with high remission and response rates, but study is only very small. There has not yet been a study comparing SAINT protocol to standard forms of TMS, therefore it is still experimental.
- Accelerated TMS protocols are being conducted by a number of groups around the world, seeking more rapid onset of action, more efficient application of treatment are in general still somewhat experimental. Increasingly evidence is supportive, including recent publication by our team with 300 patients showing equivalence of accelerated TBS protocol compared to standard TMS (*Chen L, Thomas EHX, Kaewpijit P, Miljevic A, Hughes R, Hahn L, Kato Y, Gill S, Clarke P, Ng F, Paterson T, Giam A, Sarma S, Hoy KE, Galletly C, Fitzgerald PB. Accelerated theta burst stimulation for the treatment of depression: A randomised controlled trial. Brain Stimul. 2021 Sep-Oct;14(5):1095-1105. doi: 10.1016/j.brs.2021.07.018.)*

OTHER CONDITIONS

Are we still considering all rTMS treatment for conditions other than treatment resistant depression "off label"? (Evidence for PTSD, tinnitus and other conditions seems to be mounting.)

- Most people would consider the treatment of the core symptoms of PTSD as an off-label indication – the evidence not robust enough yet to support clinical application of TMS / it remains unclear what the optimal treatment parameters should be.
- Tinnitus also in that category– the evidence not robust enough yet to support clinical application of TMS in most circumstances.
- The only other applications that have been approved by FDA based on clinical trial data are for OCD, anxiety in context of depression and smoking cessation. However, all three indications have all been with the Deep TMS Brainsway system, which is not yet available in Australia.
- Auditory hallucinations in schizophrenia is another other indication 'on the edge' of clinical application – pretty good evidence supported by multiple meta analyses, has been included in some clinical practice guidelines.

There has been researchers demonstrating fair response of LF-RDLPFC, LF-SMA, and HF-LDLPFC in OCD patients. Is it reasonable to combine the three protocols in treating treatment-resistant OCD?

If you have three unproven things, putting them together does not make them more proven. I am not yet convinced that these types of approaches are ready for mainstream use. SMA data a little more consistent than other approaches. The most evidence for TMS in OCD is for deep TMS using a specific symptom induction protocol.

Does rTMS has any role in secondary or comorbid depressive symptoms associated with addictive disorder?

In someone who is no longer drinking, TMS may be beneficial for aggressively treating depression, also in order to prevent relapse triggered by depression, and potentially some benefit in terms of cravings. Far less likely to be of benefit if the person is still drinking.

Does neuronavigation software with a patient's fMRI data provide a more specialised and sensitive method of locating the motor hotspot as well as the DLFPC because it would overcome issues due to the differences in neuroanatomy amongst patients?

There is no value in localising the motor hotspot, as this is easily done manually.

However, it may be a better way of localising DLPFC than the 5cm method, but not necessarily better beam F3 method (*see Fitzgerald, P. B. (2021). Targeting repetitive transcranial magnetic stimulation in depression: do we really know what we are stimulating and how best to do it? Brain Stimul 14(3): 730-736*).

It is challenging to justify the expense at this stage.

When establishing the RMT, is it expected for the patient to wear the cloth cap? (So motor cortex point and treatment point can be marked.)

Unnecessary but may be quite helpful when gaining experience in obtaining a RMT.

SAFETY

Where I currently work, re-titrations are only done by a select few psychiatrists, not the nursing staff. If a patient is unable to tolerate full dose despite the coil being placed correctly, are we better off ceasing treatment and having them re-titrated, or lowering the dose to a tolerable level for the session?

The broader question may be what do you do if someone is unable to tolerate the prescribed treatment – there are a number of things that can be done other than re-titration.

If the person obtaining the RMT has limited threshold experience, it may be worth going back to re-assess the threshold.

However, if the threshold is accurate, there are many things that can be done, including slight repositioning of the coil (a half centimetre medial or posteriorly) can change the sensation significantly for the patient. Reducing intensity may also be an option – recent evidence suggests treating at lower intensities may be as effective, so there is potentially room to go down. Potentially changing to low frequency right sided treatment is also an option.

I wonder what impact a gap between treatments makes? For eg. If someone wants to start treatment on Friday, but cant attend over the weekend, are they better of waiting until Monday when the treatments can be given over consecutive days? Or does the gap between treatment days not effect efficacy?

There is no available data on this. However, I would want at least 3-4 days of consecutive treatment to at least vaguely approximate what is in the literature. I would be more comfortable starting a patient on the Monday than doing a single treatment and then having a 2 day break. Although some practices conduct 7 days of treatment in a row, I would ensure there are some breaks to be consistent with the body of literature that suggests that is what is effective.

If there are deviations from this, you need to ensure that the patient is informed of the rationale for this being done, and of the limited evidence for anything other than the standard treatment course.

Non-responders – when to switch treatment type?

There is a small but inconsistent literature which doesn't really provide clear guidance on what to do if a patient is not responding and when you might consider a switch (see discussion in: Fitzgerald PB. An Update on the Clinical Use of Repetitive Transcranial Magnetic Stimulation in the Treatment of Depression, Journal of Affective Disorders, 2020; 276: 90-103. In a small trial we did, we obtained similar benefits if we just continued left high frequency treatment but this study was fairly limited.

The most commonly used options are a switch to right sided treatment or to sequential bilateral stimulation (adding right sided 1 Hz stimulation). These changes are most commonly done after 4 weeks of non-response.

TOLERABILITY

RMT - how fast can you titrate up intensity? Depends on tolerability. I start everybody at 30% and go up in 5% increments. Initial pulses are about familiarising the patient with the sensation, ensuring they are comfortable with it, relaxed, before moving up. Moving around fairly broadly initially, also in order to acclimatise the patient to the sensation.

Treatment: Start treatment low, depending on their treatment intensity – around 35-40%.

Might take 2 or 3 sessions to get up to the full treatment intensity. In my experience it is better to take a little longer to get them up to treatment intensity, rather than creating a situation where they tense up and then make the sensation more problematic for them and potentially make treatment intolerable.