School of Psychology

Information Sheet

The University of Nottingham

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Investigating combined tACS-MNS on corticospinal excitability and inhibition

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This is an invitation to take part in a one-part research study examining the role of different types of brain stimulation on cortical excitability.

Before you decide if you wish to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully.

What is the purpose of the study?

Median nerve stimulation (MNS) is a form of safe, non-invasive brain stimulation. It involves sending low intensity electrical pulses targeting a peripheral nerve in the wrist through small electrodes. It has recently been shown that MNS may be a novel treatment for Tourette Syndrome (TS), reducing tic frequency [1]. However, while this is treatment is effective in lots of individuals with TS, it is not for all.

One proposed reason for this variability is that MNS is performed without taking into account individual conditions in the brain. For example, in the brain, we all have natural brain 'waves', and these can be entrained with another safe and non-invasive form of brain stimulation called transcranial alternating current stimulation (tACS). Previous research has shown that when delivering single pulses of transcranial magnetic stimulation (TMS) to specific points of these waves, there are different cortical excitability responses depending on the point of the wave we stimulate [2-4].

This study combines tACS with MNS over the motor cortex, delivering pulses to one of two points of the wave (the peak or the trough). Cortical excitability will also be measured before and after this by applying single pulses of TMS, targeting the area of the motor cortex that controls your hand to create muscle twitches in your thumb. By measuring the strength of these twitches, we gain an indication of the level of cortical excitability in this area of the brain. We will also be measuring cortical inhibition between your sensory and motor cortex by combining single pulses of TMS with single pulses of MNS and measuring your muscle twitches. This will be completed in typically developing individuals before implementing this in individuals with TS, as it is important to understand how this stimulation works.

In summary, we will assess single pulse TMS and combined TMS-MNS pulses before and after you receive either (1) tACS only, and (2) MNS only, or (3) Combined tACS and MNS (delivered at the peak or the trough of the wave). Which session you will receive will be randomized across participants.

Do I have to take part?

It is up to you to decide whether or not to take part. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time without giving a reason. This would not affect your legal rights or affect the standard of care you receive.

If you decide to take part in this study, you will receive TMS, MNS and tACS which have temporary effects of increasing or decreasing brain cell activity. You will be asked to fill in a questionnaire which let us check that TMS, MNS and tACS will be safe for you. **TMS, MNS and tACS are safe procedures for most people, but there are a few things that we need to check first, and it is very important that you answer these questionnaires honestly.** These types of stimulation are unlikely to make you feel different and wear off within a few hours.

What will happen to me if I take part?

In this study, the researcher will greet you in reception of the School of Psychology, University of Nottingham. The researcher will first start by explaining and demonstrating TMS, MNS and tACS. We will make sure you are comfortable and understand all aspects of the study before beginning, but you are free to stop at any time. We can take multiple breaks throughout the course of the study too.

The first part of the study involves delivering some single pulses of TMS to the left side of your head, targeting the area of your brain that controls movements in your right hand. This may feel like a light tap on your head and will create a small twitch in your hand. There will also be a clicking noise for each TMS pulse. This should not be a painful experience, but some people find this strange. To measure the strength of these hand twitches, we will also attach some disposable electrodes to the skin on your hand. The researcher will find the best position to cause these muscle twitches and vary the intensity to find the threshold which causes these twitches.

After this, the researcher will attach the median nerve stimulation (MNS) electrodes to your other wrist. We will then send single pulses and find the right position and intensity of the electrodes to evoke a thumb twitch. We will then deliver about 10 minutes of single pulses of TMS and MNS of varying intensities around these threshold and measure the strength of your muscle twitches.

You will then receive **either**:

1. tACS only,
2. MNS only, and
3. Combined tACS and MNS (delivered at the peak of the wave)
4. Combined tACS and MNS (delivered at the trough of the wave)

For tACS alone, application of tACS involves applying some electrode gel to your head and attaching two electrodes encased in water-soaked sponges. Once applied and you are comfortable, the researchers will start the tACS which will last for 2 minutes. This may induce a tingly or itching sensation under the electrodes but can be stopped at any time if you feel uncomfortable.

For MNS alone, application of MNS will involve attaching two electrodes to your wrist. We will then send single pulses and find the right position and intensity of the electrodes to evoke a thumb twitch. Once this has been found and you are comfortable, the researchers will start the MNS, which involves multiple fast MNS pulses for 2 minutes. If you are uncomfortable at any point, this can be stopped.

For tACS and MNS combined, this will involve first attaching the tACS electrodes (as above) and then finding the right position and intensity of MNS to use (as above). Once these have been completed, the researcher will begin both tACS and MNS concurrently, either at the peak or the trough of the wave. This will last for 2 minutes. If you are uncomfortable at any point during this, these can be immediately stopped.

This will then be followed by the same protocol as before, where single pulses of varying intensities of TMS are delivered for about 10 minutes and the strength of muscle twitches are measured.

The session will last up to 1.5 hours.

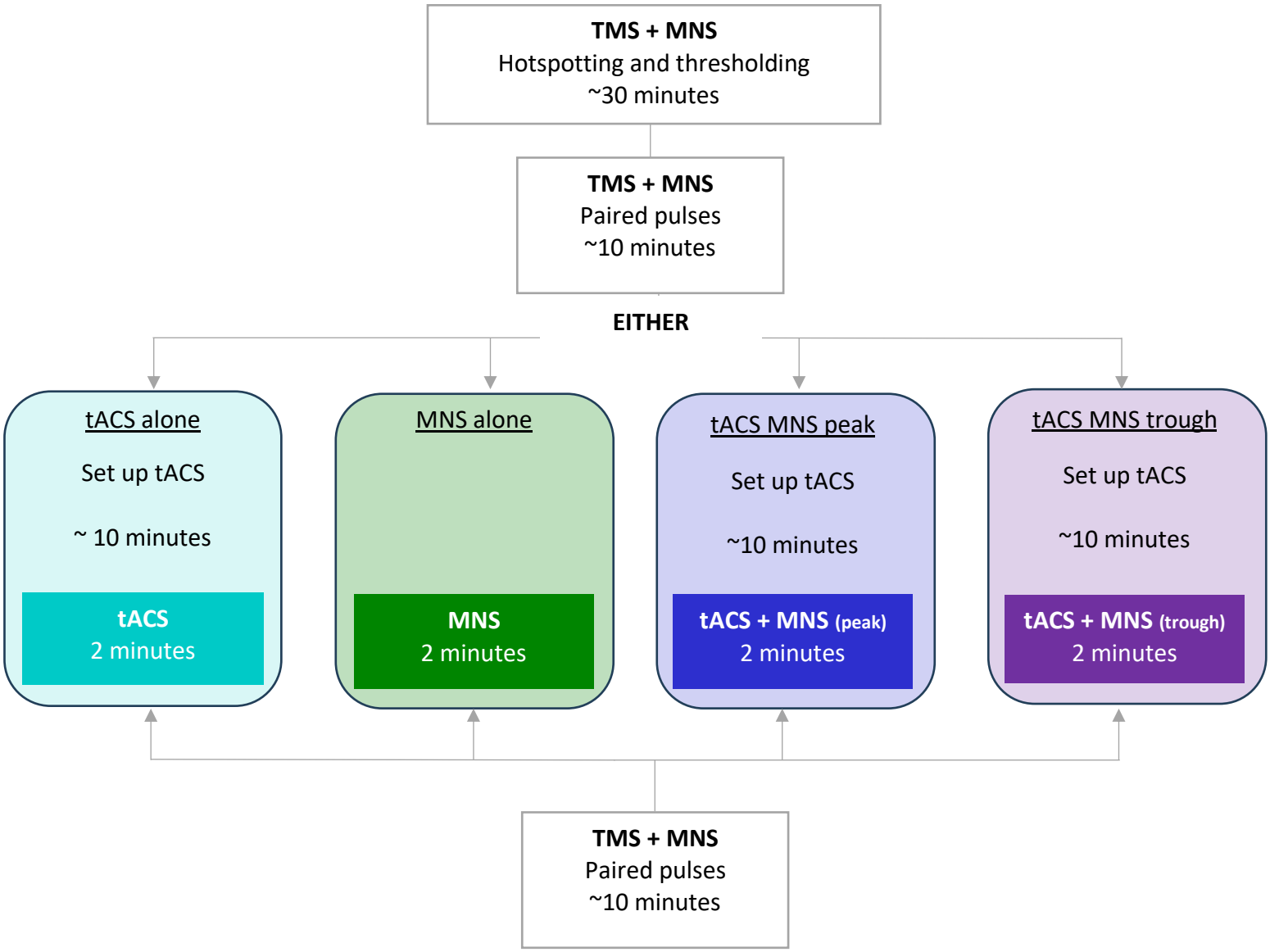

Figure 1. Diagram of study protocol

More information about TMS, tACS and MNS

TMS

TMS involves a coil being placed on the head to deliver magnetic pulses to the brain. This is a safe and painless procedure as used in the School of Psychology and has no long-term effects. TMS is a well-established neuro-stimulation technique which has been used hundreds of thousands of times and is considered to be safe. Side effects are extremely rare; however, you should be aware that there is a small risk of side effects including headache, nausea and muscle aches. In a study of 1270 TMS sessions the reporting of such side effects was 5% [5]. The most severe potential side effect is seizure, however, this has only ever been reported in an extremely small number of participants, typically when participants have been extremely fatigued or are taking certain medications [6, 7]. This study aims to test participants who are at minimal risk of experiencing any side effects of the stimulations used. Therefore, as a precaution, you will be asked to complete a safety screening questionnaire and a follow-up questionnaire to report any unexpected after-effects

Figure 2. Participant with electrodes attached to the hand and the TMS coil paced above the area which controls hand movements.

tACS

tACS is a type of transcranial electrical stimulation (tES). The application of tES involves applying gel to your head and attaching electrodes in thin water-soaked sponges. During tES stimulation, a weak current will pass through the electrodes. While stimulated, you may experience an itching, tingling, or burning sensation. tES has been used widely in research for over a decade and no serious adverse effects have been reported. Currently, the only known risks are skin irritation for participants with sensitive skin or open head wounds. In the unlikely event of you noticing any adverse effects after the stimulation you should inform the researcher. As a safety precaution,

you will have to fill in a Safety Screening Questionnaire before and an Adverse Effects Questionnaire after the experiment.

Figure 3. Participant with tACS electrodes attached to the head and TMS coil.

MNS

MNS is a non-invasive brain stimulation technique. It involves sending low intensity electrical pulses targeting a peripheral nerve in the wrist through small electrodes. Peripheral nerves are able to send signals to the brain, so by stimulating them it is possible to safely and indirectly influence brain activity. We will stimulate at safety parameters so that there are no risks. Wrist stimulation is not painful, but if you find the procedure uncomfortable, we will terminate the study immediately. We will do some tests before the study so that you can see how the stimulation feels like and if you still want to proceed with the study or not.

Figure 4. Participant with MNS electrodes attached to the hand.

Expenses and payments

Each session comes with an inconvenience allowance of £10 per hour.

Participation in this study is totally voluntary and you are under no obligation to take part. You are free to withdraw at any point before or during the study. All data collected will be kept confidential and used for research purposes only. It will be stored in compliance with the General Data Protection Regulation and Data Protection Act (2018). The researchers involved in this study are employed through the University of Nottingham and will process your personal data in order to carry out this research. The legal basis for this processing is Article 6(1e) - processing is necessary for the performance of a task carried out in the public interest. Details such as how to contact the University's Data Protection Officer and your rights as a data subject can be found at https://www.nottingham.ac.uk/utilities/privacy/privacy.aspx.

Privacy information for Research Participants

For information about the University's obligations with respect to your data, who you can get in touch with and your rights as a data subject, please visit: https://www.nottingham.ac.uk/utilities/privacy/privacy-information-for-research-participants.aspx

If you have any questions or concerns please don't hesitate to ask now. We can also be contacted after your participation.

If you have any complaints about the study, please contact:
Stephen Jackson (Chair of Ethics Committee)
stephen.jackson@nottingham.ac.uk

References:

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2. 1. Schilberg, L. et al. (2018). Phase of beta-frequency tACS over primary motor cortex modulates corticospinal excitability. Cortex, 103, 142–152. https://doi.org/10.1016/j.cortex.2018.03.001.
3. Nakazono, H., et al. (2016). Phase and frequency-dependent effects of transcranial alternating current stimulation on motor cortical excitability. University of Kyushu, https://doi.org/10.15017/1806864
4. Nakazono, H., et al. (2021). A specific phase of transcranial alternating current stimulation at the β frequency boosts repetitive paired-pulse TMS-induced plasticity. Scientific Reports, 11(1). https://doi.org/10.1038/s41598-021-92768-x
5. Maizey, L., et al. (2013). *Comparative incidence rates of mild adverse effects to transcranial magnetic stimulation.* Clin Neurophysiol, **124**(3), 536-44.
6. Rossi, S., Antal, A., Bestmann, S., Bikson, M., Brewer, C., Brockmöller, J., ... & Hallett, M. (2021). Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. *Clinical Neurophysiology*, *132*(1), 269-306. doi: 10.1016/j.clinph.2020.10.003
7. Dobek, C.E., et al. (2015). *Risk of seizures in transcranial magnetic stimulation: a clinical review to inform consent process focused on bupropion.* Neuropsychiatr Dis Treat, **11,** 2975-87.

Research participant privacy notice
Study: Investigating combined tACS-MNS on corticospinal excitability and inhibition

Privacy information for Research Participants
For information about the University's obligations with respect to your data, who you can get in touch with and your rights as a data subject, please visit: www.nottingham.ac.uk/utilities/privacy/privacy.aspx.

Why we collect your personal data
We collect personal data under the terms of the University's Royal Charter in our capacity as a teaching and research body to advance education and learning. Specific purposes for data collection on this occasion are to better understand how alterations in brain chemistry in Tourette's syndrome contribute to the occurrence and control of tics.

Legal basis for processing your personal data under GDPR
The legal basis for processing your personal data on this occasion is Article 6(1a) consent of the data subject.

Special category personal data
In addition to the legal basis for processing your personal data, the University must meet a further basis when processing any special category data, including: personal data revealing racial or ethnic origin, political opinions, religious or philosophical beliefs, or trade union membership, and the processing of genetic data, biometric data for the purpose of uniquely identifying a natural person, data concerning health or data concerning a natural person's sex life or sexual orientation.
The basis for processing your sensitive personal data on this occasion is Article 9(2a) the data subject has given explicit consent to the processing.

How long we keep your data
The University may store your data for up to 25 years and for a period of no less than 7 years after the research project finishes. The researchers who gathered or processed the data may also store the data indefinitely and reuse it in future research. Measures to safeguard your stored data include storing data with a unique ID number. This will be held separately from personal information such as your name, date of birth and address. Physical data such as questionnaire measures will be held in a locked cabinet in a locked room within the School of Psychology. Digital data including brain scans will be held on secure, password protected devices only.

Who we share your data with
Extracts of your data may be disclosed in published works that are posted online for use by the scientific community. Your data may also be stored indefinitely on external data repositories (e.g., the UK Data Archive) and be further processed for archiving purposes in the public interest, or for historical, scientific or statistical purposes. It may also move with the researcher who collected your data to another institution in the future.