School of Psychology

Information Sheet

The University of Nottingham

UNITED KINGDOM · CHINA · MALAYSIA

Investigation of the effects of phase-targeted and frequency-selective primary motor cortex inhibition during a combined tACS-TMS study

Ethics Approval Number: S1685

Researcher: Aneta Dvorakova, Dr Aikaterini Gialopsou

Supervisors: Stephen Jackson

Contact Details: Aneta.Dvorakova@nottingham.ac.uk

This is an invitation to take part in a two-part research study examining the role of different stimulation frequencies on cortical inhibition. These two sessions will be at least 3 days and at most 7 days apart.

Before you decide whether you wish to take part, it is important to understand the purpose of the research and what it will involve. Please take time to read the following information carefully.

What is the purpose of the study?

In this study, we aim to assess the differences in cortical inhibition in the primary motor cortex (the brain area responsible for movement) based on the brain's oscillatory state. This could help us explore which neuronal populations are affected by specific oscillations. This research may help establish non-invasive stimulation parameters that could potentially benefit patient populations with altered brain function.

The brain's electrical activity naturally oscillates at different frequencies, and specific frequencies are known to correlate with various functions. Transcranial alternating current stimulation (tACS) is a safe, non-invasive brain stimulation technique that, when active, can influence the natural brain's oscillations by introducing a very low (1.5 mA) electrical current into the cortex.

Transcranial magnetic stimulation (TMS) is another form of safe, non-invasive brain stimulation that can briefly modulate brain neuronal excitability and inhibition in the motor cortex by discharging a magnetic pulse. In this study, we will use single-pulse TMS to assess neuronal conductivity in the motor cortex and paired-pulse TMS to assess cortical inhibition. Recent research has shown that the efficacy of this TMS modulation depends on at which point of the natural brain wave the TMS pulse gets delivered (i.e. peak or trough) [1 ; 2 ; 3].

By combining TMS with tACS, we can target different phases of the oscillation wave and examine how motor cortex inhibition varies depending on the frequency of the

oscillation. To measure the motor cortex response, we will use electromyography (EMG), which records muscle activity via disposable electrodes placed on three areas of your right hand.

Do I have to take part?

Participation is entirely voluntary. If you decide to take part, you will be given this information sheet to keep and 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. Your decision to withdraw will not affect your legal rights or the standard of care you receive.

If you decide to take part in this study, you will be asked to complete a questionnaire to help us assess whether TMS and tACS are safe for you. These stimulation procedures are safe for most people, but there are a few factors we need to check first. It is therefore very important that you answer the questionnaire honestly.

What will happen to me if I take part?

If you take part, you will meet the researcher on the second floor of the School of Psychology at the University of Nottingham. The researcher will first explain and demonstrate TMS and tACS. You will also be asked to complete two safety questionnaires and a consent form. We will make sure you are comfortable and understand all aspects of the study before proceeding. You are free to stop at any time, and breaks can be taken throughout the study.

Initially, we will locate a motor hotspot (the area of the cortex responsible for controlling your right-hand movements) using TMS. This involves delivering single pulses of TMS to the left side of your head, which may feel like a light tap on your head and cause a small twitch in your hand. You will also hear a clicking noise with each TMS pulse. The experience should not be painful, though some people may find it strange or feel a “zing” sensation on their skin. To measure the strength of the hand twitches, we will attach disposable electrodes to the skin on your hand.

Once the hotspot has been found, we will set up the tACS electrodes on your head. Then, we will determine the minimum intensity of the TMS pulse needed to evoke a muscle response. Afterward, we will apply tACS in one of the following frequencies: **6Hz**, **10Hz**, **22Hz**, or **37Hz**, in a random order. In rare cases, tACS may induce a tingling or itching sensation under the electrodes, but we can stop at any time if you feel uncomfortable.

During each session, two stimulation blocks of different tACS frequencies will be applied. Within one stimulation block, we will measure **single-pulse** and **paired-pulse** TMS both at different phases of the oscillatory wave, in a randomised manner. Each block will last no more than 24 minutes, with approximately a 15-minute break between blocks. During the stimulation, you will be asked to keep your hand relaxed and refrain from speaking.

Please note that tACS involves applying an electrode gel to your head and attaching two electrodes encased in water-soaked sponges. We will provide shampoo, a towel, and access to either a shower or a hair-washing sink to wash your hair, if you wish.

Each session typically lasts about 2 hours, though it may occasionally extend to a maximum of 3 hours.
The next day, you will receive a follow up 24-hour post TMS stimulation questionnaire to report any unexpected after-effects.

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

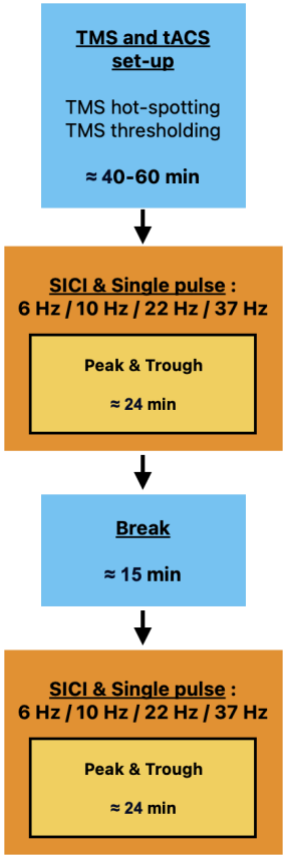

Figure 1. Diagram of study protocol

More information about TMS and tACS

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% [4]. 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 [5; 8]. 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.

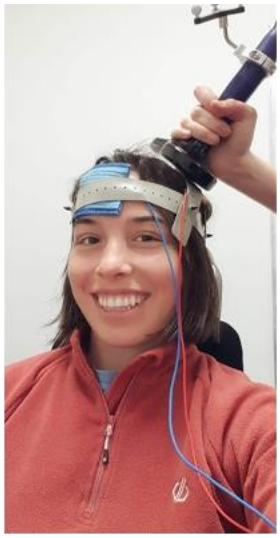

Figure 3. Participant with electrodes attached to the head.

Privacy information for Research Participants

Participation in this study is 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.

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:

1. Guerra A., Pogosyan A., Nowak M., Tan H., Ferreri F., Di Lazzaro V., & Brown P. (2016). Phase Dependency of the Human Primary Motor Cortex and Cholinergic Inhibition Cancelation During Beta tACS. *Cerebral cortex (New York, N.Y. : 1991)*, *26*(10), 3977–3990.
2. Nowak, M., Hinson, E., van Ede, F., Pogosyan, A., Guerra, A., Quinn, A., Brown, P., & Stagg, C. J. (2017). Driving Human Motor Cortical Oscillations Leads to Behaviorally Relevant Changes in Local $GABA_A$ Inhibition: A tACS-TMS Study. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *37*(17), 4481–4492.
3. Raco V, Bauer R, Tharsan S and Gharabaghi A (2016) Combining TMS and tACS for Closed-Loop Phase-Dependent Modulation of Corticospinal Excitability: A Feasibility Study. *Front. Cell. Neurosci. 10:143.*
4. Maizey, L., et al. (2013). *Comparative incidence rates of mild adverse effects to transcranial magnetic stimulation.* Clin Neurophysiol, **124**(3), 536-44.
5. Matsumoto H., Ugawa Y. (2017). Adverse events of tDCS and tACS: a review. Clin. Neurophysiol. Pract. 2, 19–25.
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.
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.*
8. Antal A., Alekseichuk I., Bikson M., Brockmöller J., Brunoni A. R., Chen R., Cohen L. G., Dowthwaite G., Ellrich J., Flöel A., Fregni F., George M. S., Hamilton R., Haueisen J., Herrmann C. S., Hummel F. C., Lefaucheur J. P., Liebetanz D., Loo C. K., McCaig C. D., Miniussi C., Miranda P. C., Moliadze V., Nitsche M. A., Nowak R., Padberg F., Pascual-Leone A., Poppendieck W., Priori A., Rossi S., Rossini P. M., Rothwell J., Rueger M. A., Ruffini G., Schellhorn K., Siebner H. R., Ugawa Y., Wexler A., Ziemann U., Hallett M., Paulus W. (2017). Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines. *Clin. Neurophysiol. 128, 1774–1809*

Standard Information Sheet Version 1 2015

Research participant privacy notice
Study: Investigation of the effects of phase-targeted and frequency-selective primary motor cortex inhibition during a combined tACS-TMS study

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.