Connectivity Effects of cTBS to the DLPFC: Examining beta phase synchronisation between the left and right DLPFC

Veronica Forslund (veronica.forslund@mrc-cbu.cam.ac.uk)
MRC Cognition and Brain Science Unit, University of Cambridge
15 Chaucer Rd, CB2 7EF, Cambridge, UK

Alexandra Woolgar (alexandra.woolgar@mrc-cbu.cam.ac.uk)
MRC Cognition and Brain Science Unit, University of Cambridge
15 Chaucer Rd, CB2 7EF, Cambridge, UK

Elizabeth Michael (elizabeth.michael@mrc-cbu.cam.ac.uk)
MRC Cognition and Brain Science Unit, University of Cambridge
15 Chaucer Rd, CB2 7EF, Cambridge, UK

Abstract

Transcranial magnetic stimulation (TMS) can induce lasting change in neural activity at both the stimulation site and brain-wide circuits. However, the efficacy of repetitive protocols in inducing brain-wide neuromodulation can vary. This pilot study used EEG to explore connectivity effects in the form of phase synchronisation between the left and right DLPFC after administration of continuous theta burst stimulation (cTBS) at the left Dorsal Lateral Prefrontal Cortex (DLPFC). To do this we used single-pulse TMS to probe connectivity effects before and after cTBS or sham cTBS. Unlike other forms of repetitive TMS (rTMS) and intermittent theta burst stimulation (iTBS), we found no change in connectivity following cTBS, highlighting the variability of neural outcomes that can follow apparently similar intervention protocols.

Keywords: Functional connectivity; DLPFC; Neurostimulation; TMS; TBS; EEG; Phase synchronization

Introduction

Transcranial magnetic stimulation (TMS) is a type of non-invasive brain stimulation that can alter neurological activity within a localised region of cortical tissue (Barker, 2017) and has recently emerged as an effective treatment for various psychiatric disorders, including major depressive disorder and obsessive-compulsive disorder (Slotema et al., 2010). A promising variant of repetitive TMS (recurring TMS pulses at a specific site) is theta burst stimulation (TBS): TBS mimics the brain's natural theta oscillations, which is thought to potentially underlie its strong efficacy and longer-lasting effects (Jannati et al., 2023; Yang et al., 2015). Different TBS types have been associated with different neurological effects. Intermittent TBS (iTBS) is associated with excitation and long-term potentiation, while continuous TBS (cTBS) is linked to inhibition and long-term depression (Chung et al., 2016; Wischnewski et al., 2015). However, the clarity of this distinction remains uncertain (Chen et al., 1997; Wasserman et al., 1996; Stoby et al., 2022). Despite research and clinical success, the full extent of the neurological mechanisms of TMS and TBS remain elusive (Kim et al., 2019).

Outside of its clinical relevance, TBS has been used to explore functional connectivity due to its efficacy influencing neural excitation (Friston et al., 1993; Friston et al., 1997, Hallett et al., 2017). Much of TBS connectivity research has focused on the motor-cortex and found evidence of phase synchronisation between motor-areas during stimulation of iTBS and cTBS, illuminating the sensorimotor network (Daskalakis et al., 2012; Johnson et al., 2012; Zrenner et al., 2018). Other TBS studies on connectivity have mainly targeted the DLPFC, often using iTBS due to its clinical relevance in treating psychiatric disorders (Blumberger et al., 2018). However, it is unclear whether cTBS can induce similar connectivity changes in the DLPFC (Woźniak-Kwaśniewska et al., 2014; Zrenner et al., 2020). Examining the connectivity effects of cTBS in the DLPFC could shed light on the neural dynamics of local DLPFC connectivity, and the neural effects of cTBS, which might differ from other rTMS interventions and thus could potentially expand the range of TMS tools in research and clinical practice.

This pilot study examined the beta phase synchronisation between left and right DLPFC following cTBS stimulation at the left DLPFC. We employed cTBS and single-pulse TMS to probe functional connectivity, with concurrent EEG. Single-pulse TMS was used to elicit a response from the targeted cortex that was not dependent on a behavioural task. Such brief interventions have been shown to evoke short-duration changes in phase synchrony as neural activity propagates through brain-wide networks (Kawasaki et al., 2014, Momi et al., 2022).

We measured phase synchronisation using the beta frequency range since beta oscillations and beta phase synchronisation in the frontal lobe have been associated with other inhibitory rTMS protocols used at the DLPFC (Zrenner et al., 2019, Zrenner et al., 2020). Compared to other measures (e.g. amplitude correlation or power changes), phase synchronization captures dynamic inter-area relationships, while minimizing false positives from volume conduction and shared sources (Vinck et al., 2011).

Method

Participants (n = 11) were asked to attend two sessions: one with sham-cTBS and one with active cTBS. Otherwise, sessions remained identical: first, two blocks of single-pulse protocol were conducted with concurrent EEG recording. A block of 96 single-pulses was used to probe neural activity, with three different intensities (40%, 100% and 110% of the participant's motor threshold). This was then followed by cTBS or sham cTBS administration (no EEG recording). Lastly, we ran two single-pulse blocks of the same design with concurrent EEG recording.

To analyse DLPFC connectivity and a frontal-occipital control, two electrode pairs were compared (DLPFC pair: F5 and F6, frontal-occipital control pair: F5 and PO7). The data were pre-processed in MATLAB using EEGLAB and custom analysis scripts (Delorme & Makeig, 2004). Data were examined in a baseline window (1000ms before single-pulse stimulation) and outcome window (1000ms after single-pulse stimulation) and averaged across the *pre* versus *post* TBS blocks in the session for each of the three single-pulse conditions. Connectivity was quantified using weighted phase lag index (wPLI) for each window separately and hence 24 wPLI measures were calculated over the two sessions for each electrode pair across the following factors and levels:

baseline/outcome window (2 levels), single-pulse intensity (3 levels: 40%, 100%, 110%), timepoint of stimulation (2 levels: pre cTBS/sham stimulation, post cTBS/sham stimulation), and session type (2 levels: active cTBS, sham cTBS).

Main analysis To test our hypothesis that cTBS affects beta phase synchronisation in the DLPFC, we examined changes in beta synchrony in the frontal electrode pair between baseline and outcome windows using a 2 x 2 x 3 repeated measures ANOVA. We predicted a three-way interaction between single-pulse intensity, stimulation timepoint and session type.

Control Analyses To control for any global effect, we conducted the same analysis on the frontal-occipital control electrode pair. To explore if the effect is frequency-specific, we repeated the analyses on an additional frequency band (alpha). Lastly, we ran control analyses using only the baseline window to assess whether the dominant effect of cTBS was to induce a baseline shift in phase synchronisation.

Results

In a 2x2x3 ANOVA to examine beta phase synchronization between the baseline and outcome windows using the frontal electrode pair, the 3-way interaction between single-pulse intensity, timepoint of stimulation and session type was not significant [$F(2,20)= 0.277$, $p= 0.761$]. There was a significant main effect of single-pulse intensity [$F(2,20)= 3.76$, $p= 0.0412$], driven by a difference between 40% and 110% of motor threshold where the 110% condition had decreased phase synchronisation in comparison to 40% [post-hoc Tukey-Kramer test: $p = 0.0347$].

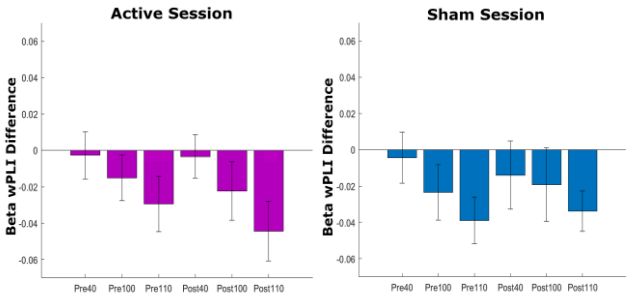

Figure 1: The x-axis shows the single-pulse intensity conditions pre- and post-TBS. The y-axis displays the frontal electrode pair beta wPLI difference (wPLI difference = baseline window wPLI – outcome window wPLI). The error bars display standard error of the mean. The graph is split by session type (active/sham).

To test whether the single-pulse effect was specific to the beta band, we ran a t-test comparing the low versus high intensity single-pulse conditions in the alpha band. The t-test for alpha was significant [$t(10) = 2.25$, $p = 0.048$], suggesting the single-pulse effect might be broadband rather than band-specific.

There were no significant results in frontal-occipital control electrode pair analyses, suggesting the single-pulse effect was not a global effect [$F(2,20)=1.05$, $p=0.368$]. Additionally, no effect was found in the baseline window for any of the analyses [all $p > .05$].

Discussion

This pilot study explored cTBS connectivity effects in the DLPFC. We observed no effect of cTBS, but found an effect of single-pulse intensity, where higher intensity seemed to increase DLPFC connectivity. A lack of altered connectivity in the DLPFC following cTBS contrasts with previous findings on the effects of other rTMS interventions in the DLPFC and the presence of cTBS connectivity effects in other parts of the cortex (Daskalakis et al., 2012; Johnson et al., 2012; Maiella et al., 2022; Zrenner et al., 2020). Further research directly comparing rTMS interventions in the same sample is needed to affirm these conclusions and expand the understanding of cTBS connectivity effects in the DLPFC and its underlying neural mechanisms.

It is possible that no effect was found due to individual variability in TMS response (Kreuzer et al., 2011; Jannati et al., 2019). Some studies have found that the timing of stimulation could influence variability, for example matching the onset of stimulation with theta oscillations seems to increase phase synchronisation (Gordon et al., 2021; Zrenner et al., 2020). Future studies could reduce variability in the data by controlling for brain state at stimulation.

A further consideration is whether the motor threshold is the optimal method for determining stimulation intensity in a repetitive protocol when targeting the DLPFC. Future studies could employ e-field mapping, which adjust the position and strength of threshold using a participant's structural scan (Park et al., 2024), to explore more effective dosing.

The change in wPLI following single pulse stimulation could be a result of a broadband evoked response (TEP, TMS-Evoked Potential). Our analysis is likely sensitive to TEPs, meaning that we cannot make claims about this effect exclusively reflecting oscillations or phase-indexed connectivity. However, later components of the TEP have been suggested to reflect the spread of activation throughout the brain (Klooster et al., 2025), which could reflect changes in network connectivity dynamics.

To conclude, this pilot study found no phase-connectivity effects of cTBS in the DLPFC. The single-pulse effect found is likely due to TEPs, which may reflect changes in network connectivity dynamics. Future studies should directly compare rTMS protocols in the same sample and use TBS stimulation protocols in relation to brain state to enable the detection of potentially subtle effects in TMS data.

Acknowledgements

This work was supported by a UKRI Medical Research Council (MC_PC_21019) grant awarded to Prof Peter Magill at University of Oxford with Co-I at MRC CBU Prof Alexandra Woolgar, and intramural funding from the UKRI Medical Research Council (MC/UU/00030/15) for the scientific programme of Prof Alexandra Woolgar.

References

Barker. (2017). Transcranial Magnetic Stimulation - past, present and future. *Brain Stimulation*, *10*(2), 540–540. https://doi.org/10.1016/j.brs.2017.01.573

Blumberger, Vila-Rodriguez, F., Thorpe, K. E., Feffer, K., Noda, Y., Giacobbe, P., Knyahnytska, Y., Kennedy, S. H., Lam, R. W., Daskalakis, Z. J., & Downar, J. (2018). Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. *The Lancet (British Edition)*, *391*(10131), 1683–1692. https://doi.org/10.1016/S0140-6736(18)30295-2

Chen, Classen, J., Gerloff, C., Celnik, P., Wassermann, E. M., Hallett, M., & Cohen, L. G. (1997). Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology*, *48*(5), 1398–1403. https://doi.org/10.1212/WNL.48.5.1398

Chung, S. W., Hill, A. T., Rogasch, N. C., Hoy, K. E., & Fitzgerald, P. B. (2016). Use of theta-burst stimulation in changing excitability of motor cortex: A systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews*, *63*, 43–64. https://doi.org/10.1016/j.neubiorev.2016.01.008

Delorme A & Makeig S (2004) EEGLAB: an open-source toolbox for analysis of single-trial EEG dynamics, Journal of Neuroscience Methods 134:9-21.

Daskalakis, Farzan, F., Radhu, N., & Fitzgerald, P. B. (2012). Combined transcranial magnetic stimulation and electroencephalography: Its past, present and future. *Brain Research*, *1463*, 93–107. https://doi.org/10.1016/j.brainres.2012.04.045

Friston, K. J., Buechel, C., Fink, G. ., Morris, J., Rolls, E., & Dolan, R. . (1997). Psychophysiological and Modulatory Interactions in Neuroimaging. *NeuroImage (Orlando, Fla.)*, *6*(3), 218–229. https://doi.org/10.1006/nimg.1997.029

Friston, K. J., Frith, C. D., Liddle, P. F., & Frackowiak, R. S. J. (1993). Functional Connectivity: The Principal-Component Analysis of Large (PET) Data Sets. *Journal of Cerebral Blood Flow and Metabolism*, *13*(1), 5–14. https://doi.org/10.1038/jcbfm.1993.4

Gordon, Dörre, S., Belardinelli, P., Stenroos, M., Zrenner, B., Ziemann, U., & Zrenner, C. (2021). Prefrontal Theta-Phase Synchronized Brain Stimulation With Real-Time EEG-Triggered TMS. *Frontiers in Human Neuroscience*, *15*, 691821–691821. https://doi.org/10.3389/fnhum.2021.691821

Hallett, Di Iorio, R., Rossini, P. M., Park, J. E., Chen, R., Celnik, P., Strafella, A. P., Matsumoto, H., & Ugawa, Y. (2017). Contribution of transcranial magnetic stimulation to assessment of brain connectivity and networks. *Clinical Neurophysiology*, *128*(11), 2125–2139. https://doi.org/10.1016/j.clinph.2017.08.007

Jannati, A., Fried, P. J., Block, G., Oberman, L. M., Rotenberg, A., & Pascual-Leone, A. (2019). Test-retest reliability of the effects of continuous theta-burst stimulation. *Frontiers in Neuroscience*, *13*(MAY), 447–447. https://doi.org/10.3389/fnins.2019.00447

Jannati, A. Oberman, L. M., Rotenberg, A., & Pascual-Leone, A. (2023). Assessing the mechanisms of brain plasticity by transcranial magnetic stimulation. *Neuropsychopharmacology (New York, N.Y.)*, *48*(1), 191–208. https://doi.org/10.1038/s41386-022-01453-8

Johnson, JS., Kundu, B., Casali, A. G., & Postle, B. R. (2012). Task-dependent changes in cortical excitability and effective connectivity: A combined TMS-EEG study. Journal of Neurophysiology, 107(9), 2383–2392. https://doi.org/10.1152/jn.00707.2011

Kawasaki, M., Uno, Y., Mori, J., Kobata, K., & Kitajo, K. (2014). Transcranial magnetic stimulation-induced global propagation of transient phase resetting associated with directional information flow. *Frontiers in human neuroscience*, *8*, 173.

Kim, T. D., Hong, G., Kim, J., & Yoon, S. (2019). Cognitive enhancement in neurological and psychiatric disorders using transcranial magnetic stimulation (TMS): a review of modalities, potential mechanisms and future implications. *Experimental Neurobiology*, *28*(1), 1.

Klooster, D., Tseng, Y.-H., Ozdemir, R., Vink, J., Inouye, S., Pascual-Leone, A., & Shafi, M. (2025). TMS propagation explained in terms of connectivity patternsTMS propagation explained in terms of connectivity patterns. *Brain Stimulation*, *18*(1), 323. https://doi.org/10.1016/j.brs.2024.12.328

Kreuzer, P., Langguth, B., Popp, R., Raster, R., Busch, V., Frank, E., Hajak, G., Landgrebe, M. (2011). Reduced intra-cortical inhibition after sleep deprivation: a transcranial magnetic stimulation study. *Neuroscience letters*, *493*(3), 63-66.

Maiella, Casula, E. P., Borghi, I., Assogna, M., D'Acunto, A., Pezzopane, V., Mencarelli, L., Rocchi, L., Pellicciari, M. C., & Koch, G. (2022). Simultaneous transcranial electrical and magnetic stimulation boost gamma oscillations in the dorsolateral prefrontal cortex. *Scientific Reports*, *12*(1), 19391–19391. https://doi.org/10.1038/s41598-022-23040-z

Momi, D., Ozdemir, R. A., Tadayon, E., Boucher, P., Di Domenico, A., Fasolo, M., Shafi, M. M., Pascual-Leone, A., & Santarnecchi, E. (2022). Phase-dependent local brain states determine the impact of image-guided

transcranial magnetic stimulation on motor network electroencephalographic synchronization. *The Journal of Physiology*, *600*(6), 1455–1471. https://doi.org/10.1113/JP282393

Park, T. Y., Franke, L., Pieper, S., Haehn, D., & Ning, L. (2024). A review of algorithms and software for real-time electric field modeling techniques for transcranial magnetic stimulation. *Biomedical Engineering Letters*, *14*(3), 393–405. https://doi.org/10.1007/s13534-024-00373-4

Slotema, C. W., Dirk Blom, J., Hoek, H. W., & Sommer, I. E. (2010). Should we expand the toolbox of psychiatric treatment methods to include Repetitive Transcranial Magnetic Stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. *Journal of Clinical Psychiatry*, *71*(7), 873

Stoby, K. S., Rafique, S. A., Oeltzschner, G., & Steeves, J. K. E. (2022). Continuous and intermittent theta burst stimulation to the visual cortex do not alter GABA and glutamate concentrations measured by magnetic resonance spectroscopy. *Brain and Behavior*, *12*(2), e2478-n/a. https://doi.org/10.1002/brb3.2478

Vinck, M., Oostenveld, R., Van Wingerden, M., Battaglia, F., & Pennartz, C. M. (2011). An improved index of phase-synchronization for electrophysiological data in the presence of volume-conduction, noise and sample-size bias. *Neuroimage*, *55*(4), 1548-1565.

Wassermann, Cohen, L., Flitman, S., Chen, R., & Hallett, M. (1996). Seizures in healthy people with repeated "safe" trains of transcranial magnetic stimuli. *The Lancet (British Edition)*, *347*(9004), 825–826. https://doi.org/10.1016/S0140-6736(96)90898-3

Wischnewski, & Schutter, D. J. L. . (2015). Efficacy and Time Course of Theta Burst Stimulation in Healthy Humans. *Brain Stimulation*, *8*(4), 685–692. https://doi.org/10.1016/j.brs.2015.03.004

Woźniak-Kwaśniewska, A., Szekely, D., Aussedat, P., Bougerol, T., & David, O. (2014). Changes of oscillatory brain activity induced by repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in healthy subjects. *Neuroimage*, *88*, 91-99.

Yang, Liu, T.-T., Song, X.-B., Zhang, Y., Li, Z.-H., Cui, Z.-H., Hao, Q., Liu, H. L., Lei, C. L., & Liu, J. (2015). Comparison of different stimulation parameters of repetitive transcranial magnetic stimulation for unilateral spatial neglect in stroke patients. *Journal of the Neurological Sciences*, *359*(1), 219–225. https://doi.org/10.1016/j.jns.2015.08.1541

Zrenner, D., Belardinelli, P., & Ziemann, U. (2018). Real-time EEG-defined excitability states determine efficacy of TMS-induced plasticity in human motor cortex. *Brain Stimulation*, *11*(2), 374–389. https://doi.org/10.1016/j.brs.2017.11.016

Zrenner, C., Gordon, P. C., Belardinelli, P., McDermott, E. J., Soekadar, S. R., Fallgatter, A. J., Ziemann, U., & Müller-Dahlhaus, F. (2020). Brain oscillation-synchronized stimulation of the left dorsolateral prefrontal cortex in depression using real-time EEG-triggered TMS. *Brain Stimulation*, *13*(1), 197–205. https://doi.org/10.1016/j.brs.2019.10.007

Zrenner, B., Gordon, P., Kempf, A., Belardinelli, P., McDermott, E., Soekadar, S., Fallgatter, A., Zrenner, C., Ziemann, U., & Dahlhaus, F. M. (2019). Alpha-synchronized stimulation of the left DLPFC in depression using real-time EEG-triggered TMS. *Brain Stimulation*, *12*(2), 532–532. https://doi.org/10.1016/j.brs.2018.12.753