A single- and paired-pulse TMS-EEG investigation of the N100 and long interval cortical inhibition in autism spectrum disorder

Brain Stimulation 15 (2022) 229–232

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

A single- and paired-pulse TMS-EEG investigation of the N100 and long interval cortical inhibition in autism spectrum disorder

An imbalance of cortical excitation/inhibition, commonly attributed to widespread dysregulation of gamma-aminobutyric acid (GABA), has been implicated in the neuropathophysiology of autism spectrum disorder (ASD) [1].

Unlike magnetic resonance spectroscopy (MRS), which indexes global metabolite concentration, transcranial magnetic stimulation (TMS) is capable of probing synaptic reactivity, and paired-pulse TMS (ppTMS) protocols are particularly relevant to GABA-ergic mechanisms. Electromyography (EMG) provides some evidence of reduced short-interval cortical inhibition $(SICI)_{EMG}$ in ASD following ppTMS to the primary motor cortex (M1). There is no evidence of long-interval cortical inhibition $(LICI)_{EMG}$ deficits in ASD at this site [2]. To our knowledge, only two studies have measured cortical reactivity in ASD using combined TMS and electroencephalography (TMS-EEG), neither of which applied ppTMS or investigated GABA-ergic mechanisms [3,4].

In the present study, both single-pulse (sp) and ppTMS-EEG protocols were applied to investigate the N100 TMS-evoked potential (TEP), and $LICI_{EEG}$ response, respectively. These outcomes have previously been implicated in $GABA_B$-ergic mechanisms [5], and are of specific interest given research into pharmacological modulation of GABA-ergic pathways in ASD [6].

TMS was applied to the right M1, right temporoparietal junction (TPJ), and right dorsolateral prefrontal cortex (DLPFC) in a group of adults with ASD (without intellectual disability) and matched neurotypical controls. The DLPFC and TPJ are widely implicated in the neuropathophysiology of ASD (Supplementary Material 1). M1 was included given the well-documented motor dysfunction in ASD.

Twenty-three (11 males, 12 females) adults with ASD and 22 (11 males, 11 females) age, sex, and IQ matched controls participated in this study. Further details are presented in Supplementary Material 2. Demographic and phenotypic summaries are presented in Supplementary Tables S1 and S2, respectively.

Stimulation was delivered using a figure-of-eight (70mm diameter) coil and two Magstim 200 stimulators connected via a BiStim device (Magstim Ltd.). All TMS was applied over a compatible EEG cap (EASYCAP GmbH) containing 20 silver-silver chloride (Ag–AgCl) sintered ring electrodes placed surrounding our predetermined regions of interest (ROIs) (refer to Supplementary Material 3.1). All stimulation was individualized to the intensity that produced an average motor evoked potential (MEP) of 1 mV (peak-to-peak amplitude; S1mV). S1mV did not differ between groups ($p = .65$). 75 single [see also: 4] and 75 paired (100 ms inter-stimulis-interval; $LICI_{100}$) TMS pulses were delivered consecutively to each site (M1, TPJ, DLPFC) in separate blocks. Refer to Supplementary Material 3.2 for detailed TMS processed and site localization protocols.

EMG data were processed in Signal 7.02, Cambridge Electronic Design, Cambridge, UK (Supplementary Material 4.1). Single- and paired-pulse TMS data were processed and analyzed offline using Matlab (R2020a; The Mathwoks, MA, USA) incorporating the EEGLAB and TESA toolboxes. For cleaning and processing details refer to Supplementary Material 4.2. Briefly, data were epoched, pulse artefact was removed, and data were then down-sampled to 1 KHz. ICA removed muscle artefacts. Data were band-pass (1–100 Hz) and bandstop (48–52 Hz) filtered, and TMS-evoked decay and noise-related activity was suppressed. Remaining artefacts were removed using a second round of ICA. Data were re-referenced to the average of both mastoids.

For spTMS, N100 was defined as the largest negative deflection occurring 90–140 ms following the TMS pulse, and average amplitude within ±5 ms either side of the detected peak was extracted and used for statistical analyses (Supplementary Material 4.3). $LICI_{EEG}$ was calculated (Supplementary Material 4.3) across the TEP (50–275 ms).

Frequentist and Bayesian analysis indicated that groups did not differ on N100 amplitude or latency at any site following spTMS. There were no group differences in $LICI_{EEG}$ at any site, and no evidence of group differences in $LICI_{EMG}$ at M1 (Refer to Supplementary Material 5, Supplementary Table S4 and Fig. S2). Graphical representations of the spTMS TEP waveform and the sp- and ppTMS rectified waveforms are presented in Fig. 1. Handedness did not affect outcomes (Supplementary Table S5).

To summarize, this study applied spTMS-EEG and ppTMS-EEG to the right M1, right TPJ, and right DLPFC in a sample of adults with ASD and matched neurotypical controls. Using this method, the results of this study do not provide evidence to indicate $GABA_B$-ergic deficits in this sample.

A recent meta-analysis of EEG and magnetoencephalography reports prolonged N/M100 latencies and reduced amplitudes in ASD during auditory processing, albeit limited to distinct elements of the component [7]. As the reviewed studies did not administer TMS, however, the difference in outcomes might be protocol/stimuli specific. A number of studies have noted an overlap between TEP components and other sensory/cognitively-evoked potentials. Biabani and colleagues [8], report a positive correlation between TEPs and peripherally-evoked sensory potentials from TMS applied to the shoulder (i.e. no transcranial stimulation), particularly for later components, post 60 ms. This indicates that TMS-EEG outcomes, particularly later components including the N100, are sensitive to somatosensory interference even when appropriate noise-

https://doi.org/10.1016/j.brs.2021.12.010

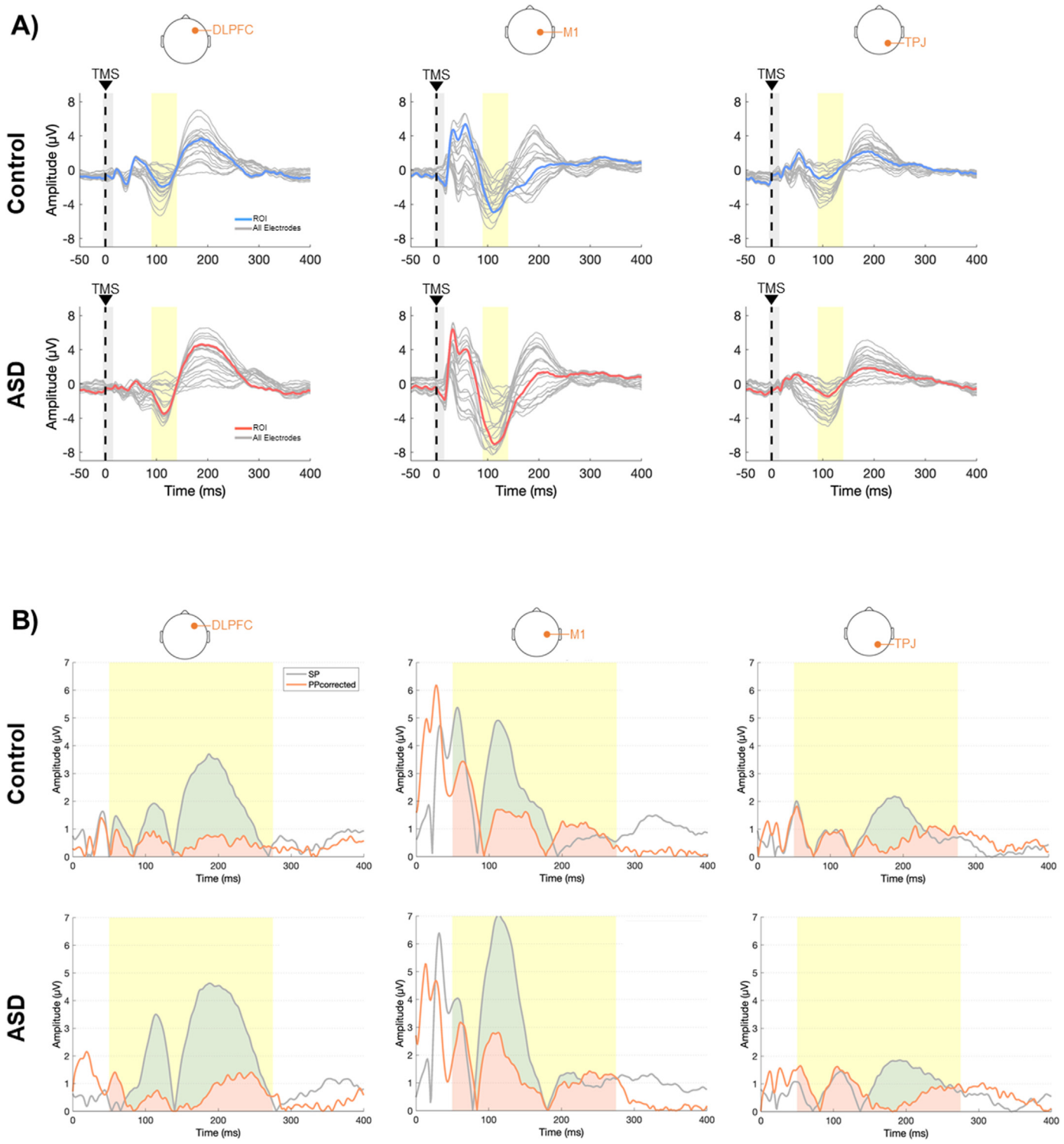

Fig. 1. A) Butterfly plots demonstrating the TMS-evoked potential (TEP) waveform for the DLPFC, M1 and TPJ post single-pulse transcranial magnetic stimulation spTMS. The thick blue (control) and red (autism spectrum disorder; ASD) lines represent the TEP waveform as an average over the ROI electrodes for each stimulation site; the thin grey lines represent all other scalp electrodes. The vertical dashed line at 0 ms indicates the TMS pulse while the surrounding grey bar represents the −5 to 15 ms section of EEG containing the large TMS artefact which was removed and re-interpolated prior to analysis. The time-window used for detection of the N100 peak is denoted by the yellow shaded bar. **B)** Graphical representation of long-interval cortical inhibition (LICI). Rectified single-pulse (SP; grey) and corrected paired-pulse (PPcorrected; orange) waveforms following ppTMS-EEG are shown. The yellow shaded bar represents the time window used for calculation of LICI. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

masking practices have been applied [8]. This raises important questions for the interpretation of this component in relation to GABA-ergic mechanisms. Further, despite a large body of evidence indirectly supporting that the TMS-induced N100 and LICI response are largely GABA-mediated, there is also evidence of acetylcholinergic and dopaminergic contributors [5].

The present findings overlap with our previous MRS-based outcomes indicating no GABAergic differences in a sub-sample of this same cohort [9]. These findings may, therefore, be sample-specific and perhaps not generalizable to younger individuals or those with increased symptom severity.

While there is considerable MRS evidence to suggest that GABA concentration is reduced in ASD [1], this is challenged by a growing body of literature using TMS to investigate GABA-related synaptic activity [2]. TMS outcomes, however, are highly variable. A recent review [10] summarizes factors potentially contributing to this variability, including, but not limited to age, handedness, [epi]genetics, biological sex/gender, and cognition.

While these preliminary findings are contrary to expectation, further research is needed. Large-scale studies investigating these mechanisms at different ages and developmental stages, as well as in individuals with various levels of ASD symptom severity, are needed. Factors contributing to variability in TMS outcomes, particularly in ASD samples, must also be elucidated. These protocols could also be incorporated with pharmaceutical trials investigating the therapeutic potential of GABA-ergic agonists in ASD to understand further the effects of such drugs at cortical regions implicated in ASD.

Funding sources

MK and ATH are supported by Alfred Deakin Postdoctoral Research Fellowships. BMF was supported by a NHMRC Early Career Fellowship (1070073). PBF is supported by a NHMRC Practitioner Fellowship (1078567). PGE is supported by a Future Fellowship from the Australian Research Council (FT160100077).

Conflict of interest statement

PBF has received equipment for research from MagVenture A/S, Medtronic Ltd, Neuronetics and Brainsway Ltd and funding for research from Neuronetics. He is on scientific advisory boards for Bionomics Ltd and LivaNova and is a founder of TMS Clinics Australia. The authors report no other conflicts of interest.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank all the participants who volunteered their time to take part in this research.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2021.12.010.

References

[1] Ajram LA, Pereira AC, Durieux AMS, Velthius HE, Petrinovic MM, McAlonan GM. The contribution of [1H] magnetic resonance spectroscopy to the study of excitation-inhibition in autism. Prog Neuro Psychopharmacol Biol Psychiatr 2019;89:236–44. https://doi.org/10.1016/j.pnpbp.2018.09.010.

[2] Masuda F, Nakajima S, Miyazaki T, Yoshida K, Tsugawa S, Wada M, et al. Motor cortex excitability and inhibitory imbalance in autism spectrum disorder assessed with transcranial magnetic stimulation: a systematic review. Transl Psychiatry 2019;9(1). https://doi.org/10.1038/s41398-019-0444-3.

[3] Jarczok TA, Fritsch M, Kröger A, Schneider AL, Althen H, Siniatchkin M, et al. Maturation of interhemispheric signal propagation in autism spectrum disorder and typically developing controls: a TMS-EEG study. J Neural Transm 2016;123(8):925–35. https://doi.org/10.1007/s00702-016-1550-5.

[4] Kirkovski M, Rogasch NC, Saeki T, Fitzgibbon BM, Enticott PG, Fitzgerald PB. Single pulse transcranial magnetic stimulation-electroencephalogram reveals No electrophysiological abnormality in adults with high-functioning autism spectrum disorder. J Child Adolesc Psychopharmacol 2016. https://doi.org/10.1089/cap.2015.0181.

[5] Tremblay S, Rogasch NC, Premoli I, Blumberger DM, Casarotto S, Chen R, et al. Clinical utility and prospective of TMS–EEG. Clin Neurophysiol 2019;130(5):802–44. https://doi.org/10.1016/j.clinph.2019.01.001.

[6] Brondino N, Fusar-Poli L, Panisi C, Damiani S, Barale F, Politi P. Pharmacological modulation of GABA function in autism spectrum disorders: a systematic review of human studies. J Autism Dev Disord 2016;46(3):825–39. https://doi.org/10.1007/s10803-015-2619-y.

[7] Williams ZJ, Abdelmessih PG, Key AP, Woynaroski TG. Cortical auditory processing of simple stimuli is altered in autism: a meta-analysis of auditory evoked responses. Biol Psychiatr: Cognit Neurosci Neuroimag 2021;6(8):767–81. https://doi.org/10.1016/j.bpsc.2020.09.011.

[8] Biabani M, Fornito A, Mutanen TP, Morrow J, Rogasch NC. Characterizing and minimizing the contribution of sensory inputs to TMS-evoked potentials. Brain Stimulation 2019;12(6):1537–52. https://doi.org/10.1016/j.brs.2019.07.009.

[9] Kirkovski M, Suo C, Enticott PG, Yücel M, Fitzgerald PB. Short communication: sex-linked differences in gamma-aminobutyric acid (GABA) are related to social functioning in autism spectrum disorder. Psychiatr Res Neuroimaging 2018;274:19–22. https://doi.org/10.1016/j.pscychresns.2018.02.004.

[10] Pellegrini M, Zoghi M, Jaberzadeh S. A checklist to reduce response variability in studies using transcranial magnetic stimulation for assessment of corticospinal excitability: a systematic review of the literature. Brain Connect 2020;10(2):53–71. https://doi.org/10.1089/brain.2019.0715.

Melissa Kirkovski*, Aron T. Hill
Cognitive Neuroscience Unit, School of Psychology, Deakin University, Geelong, Victoria, Australia

Nigel C. Rogasch
Brain, Mind and Society Research Hub, School of Psychological Sciences and Turner Institute for Brain and Mental Health, Monash University, Melbourne, Australia

Monash Biomedical Imaging, Monash University, Melbourne, Australia

South Australian Health and Medical Research Institute (SAHMRI), Adelaide, Australia

Discipline of Psychiatry, School of Medicine, University of Adelaide, Adelaide, Australia

Takashi Saeki
Department of Psychiatry, Yokohama City University School of Medicine, Yokohama, Japan

Bernadette M. Fitzgibbon
Epworth Centre for Innovation in Mental Health, Epworth HealthCare and Central Clinical School, Monash University, Melbourne, Australia

Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Australia

Joel Yang
Respiratory and Sleep Medicine, The Royal Children's Hospital, Melbourne, Australia

Cognitive Neuroscience Unit, School of Psychology, Deakin University, Geelong, Victoria, Australia

Michael Do, Peter H. Donaldson, Natalia Albein-Urios
Cognitive Neuroscience Unit, School of Psychology, Deakin University, Geelong, Victoria, Australia

Paul B. Fitzgerald
Epworth Centre for Innovation in Mental Health, Epworth HealthCare and Central Clinical School, Monash University, Melbourne, Australia

Peter G. Enticott
Cognitive Neuroscience Unit, School of Psychology, Deakin University, Geelong, Victoria, Australia

* Corresponding author. Cognitive Neuroscience Unit, School of Psychology, Deakin University Melbourne Burwood Campus, 221 Burwood Highway, Burwood, VIC, 3125, Australia.
E-mail address: melissa.kirkovski@deakin.edu.au (M. Kirkovski).

9 November 2021
Available online 29 December 2021