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Research report

Cortical inhibition of distinct mechanisms in the dorsolateral prefrontal cortex is related to working memory performance: A TMS–EEG study

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ABSTRACT

Paired-pulse transcranial magnetic stimulation combined with electroencephalography (TMS–EEG) is a method for studying cortical inhibition from the dorsolateral prefrontal cortex (DLPFC). However, little is known about the mechanisms underlying TMS-evoked cortical potentials (TEPs) from this region, let alone inhibition of these components. The aim of this study was to assess cortical inhibition of distinct TEPs and oscillations in the DLPFC using TMS–EEG and to investigate the relationship of these mechanisms to working memory. 30 healthy volunteers received single and paired (interstimulus interval = 100 msec) TMS to the left DLPFC. Variations in long-interval cortical inhibition (LICI) of different TEP peaks (N40, P60, N100) and different TMS-evoked oscillations (alpha, lower beta, upper beta, gamma) were compared between individuals. Variation in N100 slope following single pulse TMS, another putative marker of inhibition, was also compared with LICI of each measure. Finally, these measures were correlated with performance of a working memory task. LICI resulted in significant suppression of all TEP peaks and TMS-evoked oscillations (all $p < .05$). There were no significant correlations between LICI of different TEP peaks or TMS-evoked oscillations with the exception of P60 and N100. Variation in N100 slope correlated with LICI of N40 and beta oscillations. In addition, LICI of P60 and N100 were differentially correlated with working memory performance. The results suggest that both the LICI paradigm and N100 following single pulse TMS reflect complementary methods for assessing $GABA_B$-mediated cortical inhibition in the DLPFC. Furthermore, these measures demonstrate the importance of prefrontal $GABA_B$-mediated inhibitory control for working memory performance.

Abbreviations: GABA, γ-amino butyric acid; TMS, transcranial magnetic stimulation; LICI, long-interval cortical inhibition; MEP, motor evoked potential; TEP, TMS-evoked cortical potentials; EEG, electroencephalography; DLPFC, dorsolateral prefrontal cortex; APB, abductor pollicus brevis; RMT, resting motor threshold.

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1. Introduction

Cortical inhibition refers to suppression of neuronal activity and is a fundamental mechanism for both the generation and control of coordinated cortical network activity (Isaacson & Scanziani, 2011). In the mature cortex, cortical inhibition is largely governed by the neurotransmitter γ-amino butyric acid (GABA), which alters polarization of neuronal membranes via fast acting $GABA_A$ receptors and slower acting $GABA_B$-receptors (Krnjević, 1997). The dynamic properties of these receptor sub-types appear to serve different functional roles. $GABA_A$ receptors are fundamental for generating fast, coordinated network activity such as gamma oscillations (30–80 Hz) (Cardin et al., 2009; Sohal, Zhang, Yizhar, & Deisseroth, 2009; Whittington, Traub, & Jefferys, 1995), however the functional role of $GABA_B$-mediated inhibition is less clear. Recent work has suggested that $GABA_B$-mediated cortical inhibition plays an important role in modulating cortical network activity (Kohl & Paulsen, 2010). Importantly, dysfunction of $GABA_B$-mediated inhibition may play a crucial role in neurological and psychiatric conditions that are thought to result from impaired control of network activity, such as epilepsy (Schuler et al., 2001) and schizophrenia (Daskalakis & George, 2009; Rogasch, Daskalakis, & Fitzgerald, 2014).

In humans, $GABA_B$-mediated cortical inhibition can be assessed using transcranial magnetic stimulation (TMS). TMS utilizes electromagnetic induction to non-invasively depolarize excitatory and inhibitory cortical neurons across the scalp (Barker, Jalinous, & Freeston, 1985). When a suprathreshold TMS pulse is preceded by a suprathreshold conditioning pulse at intervals of 50–200 msec (i.e., paired-pulse TMS), TMS-evoked neuronal activity is suppressed through a process known as long-interval cortical inhibition (LICI). This can be measured as either a decrease in motor cortical output via motor evoked potentials (MEPs) in peripheral muscles (Nakamura, Kitagawa, Kawaguchi, & Tsuji, 1997; Valls-Solé, Pascual-Leone, Wassermann, & Hallett, 1992) or modulation of TMS-evoked cortical potentials (TEPs) assessed directly from the cortex using electroencephalography (EEG) (Daskalakis, Farzan, Barr, Maller, et al., 2008; Fitzgerald et al., 2008). In addition to paired-pulse paradigms, a growing body of evidence suggests that the N100, a negative TEP, also represents $GABA_B$-mediated inhibitory function. For instance, different motor tasks modulate N100 amplitude in a way consistent with cortical inhibition (Bonnard, Spieser, Meziane, de Graaf, & Pailhous, 2009; Bruckmann et al., 2012; Kicić, Lioumis, Ilmoniemi, & Nikulin, 2008; Nikulin, Kicic, Kahkonen, & Ilmoniemi, 2003; Spieser, Meziane, & Bonnard, 2010), N100 amplitude correlates with motor measures of inhibition including LICI (Rogasch, Daskalakis, & Fitzgerald, 2013) and the silent period (Farzan et al., 2013) and the N100 over motor cortex is specifically increased by a $GABA_B$-receptor agonist (Premoli et al., 2014).

Although useful for studying motor physiology, the real strength of combined TMS–EEG is in studying mechanisms outside the motor cortex. LICI of both TMS-evoked activity (Fitzgerald et al., 2008; Fitzgerald, Maller, Hoy, Farzan, & Daskalakis, 2009; Daskalakis, Farzan, Barr, Maller, et al., 2008) and TMS-evoked oscillations (Farzan et al., 2010a, 2009) has been demonstrated from the dorsolateral prefrontal cortex (DLPFC) using TMS–EEG. In addition, prefrontal LICI strength correlates with individual performance on a working memory task (Daskalakis, Farzan, Barr, Rusjan, et al., 2008; Hoppenbrouwers et al., 2013), providing preliminary evidence for a role of $GABA_B$-mediated inhibition in cognition. However, little is known about the mechanisms that underlie TEPs or TMS-evoked oscillations from the DLPFC, let alone inhibition of these measures. In addition, it remains unclear whether LICI suppresses TMS-evoked outputs to other cortical regions as well as local activity.

The majority of studies assessing LICI from the DLPFC have collapsed analysis across time, removing information on distinct mechanisms made possible by analysing specific TEP peaks. Therefore, the aim of this study was to compare LICI of distinct TEP peaks and TMS-evoked oscillatory bands in the DLPFC and to assess the physiological and functional relevance of these measures. We assessed natural variation in LICI strength across a population of healthy volunteers using single and paired-pulse TMS–EEG. First, we assessed whether variation in LICI of different TEP peaks and different TMS-evoked oscillations from DLPFC were related or independent. Second, we evaluated whether the N100 slope following single-pulse TMS was associated with LICI of TEPs and LICI of TMS-evoked oscillations. Third, we assessed whether LICI suppressed TMS-evoked activity and oscillations across the scalp as well as at the site of stimulation. Finally, to assess the functional relevance of these measures, we investigated the relationship between inhibition in DLPFC and working memory performance.

2. Materials and methods

2.1. Participants

30 volunteers participated in the current study (32.2 ± 11 years, 8 female). Volunteers had no history of neurological or psychiatric illnesses and provided informed written consent before commencement of the study. All experimental procedures were approved by the Monash University, Alfred Hospital and Centre for Addiction and Mental Health Human Research Ethics Committees in accordance with the declaration of Helsinki.

2.2. Procedures

Participants were seated comfortably with their hands resting in their lap. An EEG cap was fitted to their head and electrodes were placed over the right abductor pollicus brevis (APB) muscle for electromyographic recordings. Resting motor threshold (RMT) and the TMS intensity required to evoke an MEP of ~1 mV were then determined over the motor cortical region that produced the largest responses in APB. Following motor measures, the coil was positioned so the centre rested between the F3 and F5 electrode and the handle was rotated to a 45° angle relative to midline, producing a posterior–anterior