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Research report

# Variations in response control within at-risk gamblers and non-gambling controls explained by GABAergic inhibition in the motor cortex

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ABSTRACT

Paired-pulse Transcranial Magnetic Stimulation (TMS) is used to study inhibitory and excitatory mechanisms in the motor cortex through the measurement of short-interval intracortical inhibition (SICI), indicative of GABAergic activity, and intracortical facilitation (ICF), indicative of glutamatergic activity. In the present study, TMS was delivered to the left motor cortex of 40 participants while we measured SICI and ICF at rest. We were interested in whether variation between individuals in these modulatory mechanisms is related to inhibitory control over responding measured as stop signal reaction time (SSRT). Within the same group of participants, we investigated whether SICI, ICF, SSRT, and self-reported impulsivity, are impaired in participants identified as At-Risk gamblers (n = 20) compared to non-gambling controls (n = 20). We found a significant negative correlation between SICI strength and SSRT, but no correlation between ICF strength and SSRT after controlling for the correlation between SICI and SSRT. Thus, poor inhibitory control of responding was associated with weak GABAergic activity. When taking into account the effects of substance/alcohol use and attention-deficit hyperactivity disorder (ADHD) symptom severity, At-Risk gamblers showed elevated self-reported impulsivity, but did not differ from controls on SSRT or SICI/ICF. Our study is the first to show that individual differences in motor cortex inhibition can predict stopping performance, and the first to investigate paired-pulse TMS parameters (together with other impulse control measures) in a gambling population.



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## 1. Introduction

### 1.1. *Transcranial Magnetic Stimulation and inhibitory control*

Inhibitory control is an aspect of executive functioning which involves our ability to delay, withhold or interrupt inappropriate responses. Inhibiting inappropriate responses is an important part of daily life, as it allows us to consider the consequences of a behaviour, to stop or withhold the behaviour, and then select behaviours which are more appropriate in that context.

Transcranial Magnetic Stimulation (TMS) has provided techniques that can be used to measure inhibitory processes in the brain. A peripheral muscle response can be obtained when a single pulse of TMS is applied to the primary motor cortex (M1), with the strength of this response measured as a motor evoked potential (MEP). The peak-to-peak amplitude of this MEP represents the total activation or excitability of the corticospinal motor system (Terao & Ugawa, 2002). While single pulses of TMS can probe corticospinal excitability, protocols that deliver paired pulses of TMS can reveal modulatory influences within M1 that inhibit or facilitate corticospinal output. In these protocols, the first pulse ("S1") is usually subthreshold in producing an MEP, while the second pulse ("S2") is usually suprathreshold in producing an MEP. If the interval between these pulses is very short (1–5msec), the delivery of S1 attenuates the MEP elicited by S2, an effect known as short-interval intracortical inhibition (SICI). If the interval between these pulses is slightly longer (10–30msec), the delivery of S1 facilitates the MEP elicited by S2, an effect known as intracortical facilitation (ICF). Fig. 1 shows electromyography (EMG) recordings demonstrating SICI and ICF.

SICI and ICF effects are mediated by distinct neuronal circuits within M1 (Paulus et al., 2008; Ziemann, Chen, Cohen, & Hallet, 1998; Ziemann, Lonnecker, Steinhoff, & Paulus, 1996). SICI is believed to be mediated by $GABA_A$ neurotransmission, based on evidence that $GABA_A$ agonists, such as benzodiazepines, increase SICI. ICF, on the other hand, most likely involves glutamatergic neurotransmission, as NMDA receptor antagonists, such as dextromethorphan, can reduce ICF. The GABAergic (SICI) or glutamatergic (ICF) activity is believed to originate from interneurons in the motor cortex (Kujirai et al., 1993) that are particularly sensitive to TMS and therefore can be activated by the weaker TMS pulse (S1) that is below threshold for eliciting an MEP from corticospinal output neurons. Both the GABAergic and glutamatergic interneurons converge onto a common population of cortical neurons that have higher activation thresholds and therefore are only activated by S2. However, while both GABAergic and glutamatergic interneurons have low thresholds for activation by TMS, they differ in the speed of their effect, with the GABAergic interneurons having an effect within 6 msec of activation by TMS, while the glutamatergic interneurons have their peak effect 10–30 msec after activation. Because of their distinctive time courses, both the SICI and ICF protocols have been widely used to measure the amount of local GABAergic inhibitory activity and glutamatergic facilitatory activity in the motor cortex.

Although the neurophysiological underpinnings of SICI and ICF are relatively well understood, their involvement in certain aspects of behaviour is still an important area of research. In a recent study by Du, Summerfelt, Chiappelli, Holcomb, and Hong (2014), participants showed consistent levels of SICI and ICF across two TMS sessions, suggesting that paired-pulse protocols may reveal trait-like information about differences between individuals in activity within the motor cortex. However, the functional implications of this remain unclear. One possibility is that SICI and ICF capture meaningful information about an individual's behavioural ability to suppress a response. One of the most widely used behavioural tasks for measuring response suppression is the Stop Signal Task (Logan & Cowan, 1984), which tests an individual's ability

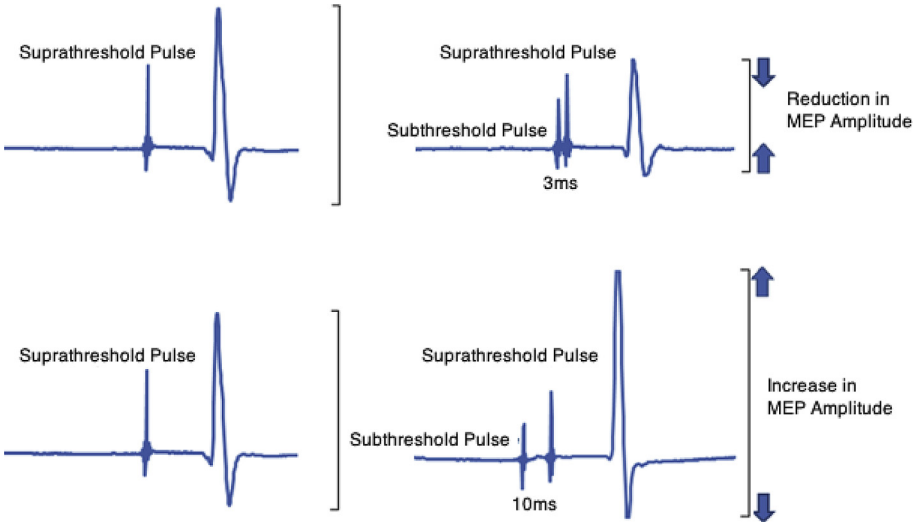


**Fig. 1 – EMG recordings demonstrating short-interval intracortical inhibition (SICI; top) and intracortical facilitation (ICF; bottom). The MEP amplitude evoked by a suprathreshold pulse (S2) is suppressed when that pulse is preceded by a subthreshold pulse (S1) at a very short interval (e.g., 3 msec), but the MEP elicited by S2 is augmented when S2 is preceded by a subthreshold S1 pulse at a longer interval (e.g., 10 msec).**