Neuroscience 312 (2016) 19–25

THE INFLUENCE OF SHORT-INTERVAL INTRACORTICAL FACILITATION WHEN ASSESSING DEVELOPMENTAL CHANGES IN SHORT-INTERVAL INTRACORTICAL INHIBITION☆

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Abstract—*Objective:* Measures of short-interval intracortical inhibition (SICI) can be contaminated by excitatory influences of short-interval intracortical facilitation (SICF), unless examined at individually-optimized interstimulus intervals (ISIs). We hypothesized that age-related differences in SICF would explain previously reported reduced SICI in children and adolescents compared with adults. *Methods:* Fifty-one participants, aged 8–29 years, underwent transcranial magnetic stimulation. SICF curves were constructed to determine the ISI at which SICF was minimal (i.e. the first trough). SICI curves were constructed at this individually-determined ISI with conditioning stimulus (S1) intensities of 60–110% of active motor threshold. *Results:* There was no effect of age on the ISI corresponding with the SICF trough. However, there was a main effect of age on the amplitude of the conditioned motor-evoked potential at the different ISIs, such that children aged 8–12 years demonstrated greater SICF than those aged 16–18 and 19–21 years. There was no effect of age on SICI, and no interaction between age group and S1 intensity. *Conclusions:* Compared with that in older adolescents and young adults, SICF is enhanced in children aged 8–12 years. Surprisingly, this enhanced SICF does not appear to reduce the degree of SICI that can be evoked at the first trough in this age group. *Significance:* This is the first report of enhanced SICF in young children. It remains possible that enhanced SICF may have confounded earlier reports of reduced SICI in children less than 8 years.

Key words: children, transcranial magnetic stimulation, motor-evoked potential, paired-pulse TMS, gamma-aminobutyric acid.

INTRODUCTION

In humans, motor cortical output is the result of complex interactions between inhibitory and excitatory processes (Chen, 2004). The balance of these processes plays an important role in the preparation and execution of motor tasks (Ridding et al., 1995; Sinclair and Hammond, 2008) and in the modulation of activity-dependent neuroplasticity in the human primary motor cortex (M1) (Sanes and Donoghue, 2000). Transcranial magnetic stimulation (TMS) is a neurophysiological technique that can be employed to study cortical circuitry in the intact human brain. Paired-pulse TMS, in particular, can be applied according to well-established parameters to test inhibitory and excitatory neuronal circuits within M1 (Rothwell, 1997). However, the majority of studies investigating these circuits in humans have included only adults, and as a consequence less is known about the balance of intracortical excitation and inhibition in children and adolescents.

Short-interval intracortical inhibition (SICI) is an established paired-pulse TMS measure of intracortical inhibition (Kujirai et al., 1993). The amplitude of the motor-evoked potential (MEP) elicited by a suprathreshold TMS pulse (S2) is suppressed if preceded by 1–6 ms by a subthreshold conditioning stimulus (S1). This inhibition is thought to be mediated by the gamma-aminobutyric acid (GABA) A receptor (Ziemann et al., 1996; Di Lazzaro et al., 2006; Florian et al., 2008), with pharmacological studies demonstrating that SICI is increased by drugs that augment the transmission of GABA (Ziemann et al., 1996, 1996), but unaffected by drugs that block voltage-gated sodium channels (Ziemann et al., 1996; Chen et al., 1997). Studies of the maturation of the GABAergic system have shown that during fetal neurodevelopment, GABA initially behaves as an excitatory neurotransmitter, but switches to become inhibitory during the early postnatal period due to a complex series of events, including the lowering of intracellular chloride concentrations (Jensen et al., 2000; Ganguly et al., 2001; Ben-Ari, 2002; Swanwick et al., 2006; Klueva et al., 2008; Ben-Ari et al., 2012). Little is known about the signaling that instigates this change or the time course of this postnatal transformation in humans. There is, however, some evidence that GABAergic inhibitory circuits undergo maturation during childhood, and some authors have

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Abbreviations: aMT, active motor threshold; ANCOVA, analysis of covariance; EMG, electromyogram; FDI, first dorsal interosseous; GABA, gamma-aminobutyric acid; ISI, interstimulus interval; M1, primary motor cortex; MEP, motor-evoked potential; rMT, resting motor threshold; SI, stimulation intensity; SICF, short-interval intracortical facilitation; SICI, short-interval intracortical inhibition; TMS, transcranial magnetic stimulation.

http://dx.doi.org/10.1016/j.neuroscience.2015.10.057
0306-4522/

hypothesized that reduced inhibition in early life enhances neuroplasticity and thereby facilitates motor learning (Mall et al., 2004; Walther et al., 2009).

Two previous studies have both reported reduced SICI in children and adolescents when compared to adults (Mall et al., 2004; Walther et al., 2009). Other studies have compared SICI in healthy children and children with attention-deficit-hyperactivity disorder and/or tic disorder, and while these studies did not compare SICI in children and adults, they provide evidence of intracortical inhibitory processes in 8–17-year-old children and adolescents (Moll et al., 1999, 2000, 2001). However, measures of SICI can be contaminated by facilitatory influences unless tested with stimulation parameters individually optimized to minimize this (Peurala et al., 2008).

The strength of intracortical facilitatory circuits can be tested using a paired-pulse TMS paradigm, where S1 is suprathreshold and S2 is sub- or suprathreshold (Ziemann et al., 1998). Strong facilitatory interaction between the paired stimuli is seen when the interstimulus interval (ISI) is ~1.5, ~2.5, and ~4.5 ms, and this has been termed short-interval intracortical facilitation (SICF) (Tokimura et al., 1996; Ziemann et al., 1998; Di Lazzaro et al., 1999; Hanajima et al., 2002; Ilic et al., 2002). In between these discrete SICF peaks are troughs, where little or no facilitation occurs. Under certain conditions, measurement of SICI can be contaminated by SICF and the consequence is a net response, reflecting the summation of SICI and SICF (Peurala et al., 2008). Consequently, these authors suggested that the contamination of SICI by SICF should be carefully avoided by assessing SICI at an individually-determined ISI that corresponds with a SICF trough. SICF is believed to be the product of S2 directly exciting the axon initial segments of excitatory intracortical interneurons previously depolarized, and made hyperexcitable, by S1 (Hanajima et al., 2002; Ilic et al., 2002). While the reduced SICI in children and adolescents compared with adults has been attributed to protracted maturation of GABAergic inhibition (Mall et al., 2004; Walther et al., 2009), the developmental trajectory of SICF circuitry has not been studied. Due to the overlap between SICI and SICF measures, it is possible that protracted SICF maturation could, at least in part, contribute to the previously reported age-related differences in SICI.

We hypothesized that the reduced SICI previously reported in children and adolescents is confounded by the influence of concomitant SICF. Therefore, we aimed to examine the influence of age on the ISI at which the first SICF trough was evident in participants aged 8–29 years. Thereafter, we constructed each individual's SICI curve at their individually-determined ISI, using S1 intensities ranging from 60% to 110% of active motor threshold (aMT), and assessed the degree of SICI induced.

EXPERIMENTAL PROCEDURES

Subjects

A total of 51 neurologically healthy subjects (mean age ± SD, 17.7 ± 4.4 years, range: 8–29 years, 20 males) participated in this study. All were born at term, as we have previously shown persistent reductions in corticomotor excitability in children and adolescents born prior to 37 completed weeks of gestation (Pitcher et al., 2012). Only right-handed participants were included in the study [handedness was confirmed with the Edinburgh Handedness Inventory Oldfield, 1971]. Prior to their inclusion in the study, participants were screened for contraindications to TMS (Rossi et al., 2009), and provided written informed consent. Parents/caregivers provided consent for participants < 18 years of age, and accompanied them to the experimental session. Exclusion criteria also included any history of perinatal brain injury or neuropathy. All procedures were approved by the Women's and Children's Health Network and University of Adelaide Human Research Ethics Committees, and all procedures were conducted in accordance with the Declaration of Helsinki (2008 revision).

Recording procedures

Participants were seated in an armchair with their hands and forearms supported. Adhesive Ag/AgCl electrodes were applied to the skin overlying the right first dorsal interosseous (FDI) hand muscle, using a belly-tendon montage. Electromyogram (EMG) signals were amplified (×1000), bandpass filtered (20–1000 Hz) (D360; Digitimer, Welwyn Garden City, UK) and then digitized at 5.1 kHz (CED 1401; Cambridge Electronic Design, Cambridge, UK), before being stored on a computer for offline analysis.

TMS

Motor cortical excitability was assessed with single- and paired-pulse TMS, applied to the left hemisphere through a figure-of-eight coil (90 mm external wing diameter) connected to two monophasic Magstim 200^2 magnetic stimulators coupled using a Magstim Bistim module (Magstim Co, Whitland, UK). The coil was oriented with the handle pointing posterolaterally at a 45° angle to the sagittal plane (i.e. posterior-anterior current flow across M1). The optimal scalp site for consistently evoking MEPs in the FDI was determined and marked with a water-soluble pen.

The resting motor threshold (rMT) was determined as the lowest TMS intensity required to evoke MEPs of at least 50 μV peak-to-peak amplitude in the resting FDI, in at least five of ten consecutive trials. The aMT was assessed while the subject maintained a voluntary contraction of approximately 10% of their maximal voluntary contraction for FDI. The aMT was determined as the lowest TMS intensity required to evoke MEPs of at least 200 μV peak-to-peak amplitude in the active FDI, in at least five of ten consecutive trials. The TMS intensity that evoked MEPs of ~1 mV peak-to-peak amplitude ($SI_{1\ mV}$) was also determined.

SICF

SICF was assessed utilizing a standard paired-pulse TMS paradigm (Ziemann et al., 1998; Peurala et al., 2008). S1 was set at $SI_{1\ mV}$, and was applied prior to S2, which was