Brain Stimulation 8 (2015) 926–936

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Original Articles

Age-related Differences in Pre- and Post-synaptic Motor Cortex Inhibition are Task Dependent

George M. Opie [a], Michael C. Ridding [b], John G. Semmler [a,*]

[a] Discipline of Physiology, School of Medical Sciences, The University of Adelaide, Adelaide, South Australia 5005, Australia
[b] Robinson Research Institute, School of Paediatrics and Reproductive Health, The University of Adelaide, Adelaide, Australia

ARTICLE INFO

Article history:
Received 6 February 2015
Received in revised form
23 March 2015
Accepted 7 April 2015
Available online 2 May 2015

Keywords:
Transcranial magnetic stimulation
Pre-synaptic inhibition
Gamma-aminobutyric acid
Task
Age

ABSTRACT

Background: Previous research has shown age-related differences in short- (SICI) and long-interval intracortical inhibition (LICI) in both resting and active hand muscles, suggesting that healthy ageing influences post-synaptic motor cortex inhibition. However, it is not known how the ageing process effects the pre-synaptic interaction of SICI by LICI, and how these pre- and post-synaptic intracortical inhibitory circuits are modulated by the performance of different motor tasks in older adults.
Objective: To examine age-related differences in pre- and post-synaptic motor cortex inhibition at rest, and during index finger abduction and precision grip.
Methods: In 13 young (22.3 ± 3.8 years) and 15 old (73.7 ± 4.0 years) adults, paired-pulse transcranial magnetic stimulation (TMS) was used to measure SICI (2 ms inter-stimulus interval; ISI) and LICI (100 and 150 ms ISI), whereas triple-pulse TMS was used to investigate SICI when primed by LICI.
Results: We found no age-related difference in SICI at rest or during index finger abduction, but significantly greater SICI in older subjects during precision grip. Older adults showed reduced LICI in resting muscle (at an ISI of 150 ms), with no age-related differences in LICI during either task. When SICI was primed by LICI, disinhibition of motor cortex was reduced in older adults at rest (100 ms ISI) and during index finger abduction (150 ms ISI), but not during precision grip.
Conclusions: Our results support age-related differences in pre- and post-synaptic motor cortex inhibition, which may contribute to impaired hand function during task performance in older adults.

Introduction

Motor deficits are a major aspect of the ageing process that can significantly impede the performance of essential activities of daily living. Subsequently, age-related deficits in motor function may lead to reduced independence, decreased quality of life and institutionalization [1]. Despite this, our understanding of how the ageing process affects function within core components of the motor system, such as the motor areas of the brain, is somewhat rudimentary. Nonetheless, within the primary motor cortex (M1), age-related changes in inhibitory neurotransmission mediated by γ aminobutyric acid (GABA) have been increasingly investigated as a factor potentially contributing to age-related motor deficits (for review, see Ref. [2]). This line of investigation stems from the established importance of intracortical inhibition in motor control [3–6] and has been facilitated by the use of non-invasive transcranial magnetic stimulation (TMS).

In humans, TMS allows an assessment of distinct GABAergic processes by applying pairs of magnetic stimuli to M1 (paired-pulse TMS), or an assessment of interactions between GABAergic processes by applying 3 magnetic stimuli to M1 (triple-pulse TMS). During paired-pulse TMS, application of a subthreshold conditioning stimulus at short-intervals (1–5 ms) prior to a suprathreshold test stimulus produces inhibition of the test motor evoked potential (MEP) via activation of post-synaptic $GABA_A$ receptors [7]. This process is known as short-interval intracortical inhibition (SICI; [8]). However, when both stimuli are suprathreshold and separated by a long inter-stimulus interval (100–150 ms; ISI), inhibition of the test MEP is thought to involve post-synaptic $GABA_B$ receptors [9] and is known as long-interval intracortical inhibition (LICI; [10]). During triple-pulse TMS, the

This study forms part of the PhD of George Opie, who is supported by an Australian Postgraduate Award Scholarship and an Adelaide Centre for Neuroscience Research Scholarship.
Disclosures: The authors declare no conflict of interest.
* Corresponding author. Tel.: +61 8 8313 7192; fax: +61 8 8313 4398.
E-mail address: john.semmler@adelaide.edu.au (J.G. Semmler).

http://dx.doi.org/10.1016/j.brs.2015.04.001
1935-861X/

interaction between LICI and SICI is assessed by preceding the conditioning and test stimuli for SICI by the conditioning stimulus for LICI [11]. This protocol results in reduced inhibition of the test MEP and is thought to involve activation of pre-synaptic $GABA_B$ receptors [9,11–14].

In young subjects, activity-dependent changes in both SICI [3,4,6] and LICI [15,16] are well established. Furthermore, the nature of this modulation is thought to be task-dependent [17,18]. In contrast, task-related changes in inhibition in older adults have been limited to measurements made during tonic contractions [19,20] or in the period prior to contraction [21–23]. However, some evidence suggests that the task-dependency of inhibitory tone in M1 is modified by age [24]. Interestingly, task-dependent changes in SICI and LICI have been suggested to be mediated by pre-synaptic mechanisms [18], suggesting that effects of age on the task-dependent modulation of inhibition may be influenced by changes in pre-synaptic motor cortex inhibition.

Pre-synaptic inhibition in M1 has not been previously compared between young and old adults. However, Chu and colleagues [25] investigated LICI-SICI interactions in a group of older adults (age 54–68 years) using two ISIs of 100 ms and 150 ms. While this study observed the expected reduction in inhibition using the 100 ms ISI, no change in inhibition was seen when the 150 ms interval was used [25]. However, subsequent investigations assessing the duration of pre-synaptic inhibition in young subjects have shown that effects can last >200 ms [26]. Comparing the findings of these studies suggests that LICI-SICI interactions are reduced by the ageing process, but only at longer ISIs (i.e., 150 ms). This observation may reflect a timing-dependent reduction in pre-synaptic inhibition in M1.

The aim of the current study was therefore to compare the magnitude of SICI, LICI and LICI-SICI interactions between young and old subjects during relaxation, index finger abduction and precision grip (between the index finger and thumb) – tasks that have previously produced specific changes in intracortical inhibition in young subjects [18]. Also, as effects of age on pre-synaptic motor cortex inhibition were expected to be timing-dependent, LICI-SICI interactions were assessed using two ISIs of 100 ms and 150 ms. Based on previous studies [25,26], we expected that old subjects would show reduced pre-synaptic M1 inhibition at 150 ms. Furthermore, as the activity-dependent modulation of inhibitory tone is reduced in older adults [23], we expected that task-dependent changes in this modulation would also be influenced by advancing age.

Materials and methods

15 old (73.7 ± 4.0 years) healthy subjects were recruited to participate in the current study via advertisements placed in local media. These data were compared to those from 13 young (mean ± standard deviation; 22.3 ± 3.8) healthy subjects, the results of which have been presented previously [27]. Exclusion criteria included a history of stroke, history of neurological or psychiatric disease, or current use of psychoactive medication (sedatives, antipsychotics, antidepressants etc.). Hand preference and laterality was assessed using the Edinburgh Handedness Inventory [28]. Each subject provided written, informed consent prior to participation. All experimentation was approved by the University of Adelaide Human Research Ethics Committee and conducted in accordance with the declaration of Helsinki.

Experimental arrangement

For the duration of each experimental session, subjects were seated in a comfortable chair with their right arm abducted approximately 45° at the shoulder. This allowed the forearm and hand to sit comfortably on an arm support placed next to them. Surface electromyography (EMG) was used to record responses from the first dorsal interosseous (FDI) muscle of the right hand. Two Ag–AgCl electrodes (1.6 cm diameter) were attached to the skin over the muscle in a belly-tendon montage, with a strap around the wrist grounding the electrodes. EMG was amplified (300×) and band-pass filtered (20 Hz high pass, 1 kHz low pass) using a CED1902 (Cambridge Electronic Design, Cambridge, UK), and digitized at 2 kHz using a CED1401 interface (Cambridge Electronic Design), before being recorded and stored offline for analysis. To facilitate muscle relaxation when required, real-time EMG signals were displayed under high gain (50 μV/division) on an oscilloscope placed in front of the subject.

Each subject participated in two experimental sessions held on separate days, each of 2–3 h duration. Within each session, TMS was applied during complete relaxation of FDI and while FDI was active in producing one of two low intensity (5% of maximum force) contractions, performed in random order. For one of the sessions, subjects were required to produce an isolated abduction of the index finger, whereas in the other session they were required to perform a precision grip of the index finger and thumb. As prolonged contractions were required to complete the multiple stimulation conditions needed for triple-pulse TMS (see below), assessing each active task on separate days reduced the likelihood of fatiguing the target muscle, which may have confounded measurements of intracortical inhibition [29–31]. Within each experimental session, all TMS conditions (see below) were applied twice, once with the target muscle at rest, and again with the target muscle active (either abduction or precision grip). Furthermore, paired-pulse TMS was always performed before triple-pulse TMS for all subjects, allowing the experimenter to monitor baseline levels of inhibition before applying triple-pulse TMS. During active state measurements, stimulation began after subjects had reached stable force application.

Experimental procedures

Maximal voluntary contraction

At the beginning of each experiment, maximum voluntary contractions (MVC) were assessed for each subject. This was performed for both index finger abduction and precision grip using the index finger and thumb. During index finger abduction, the subject's right hand was positioned with the palm facing downwards and the index finger isolated from the middle, ring and little fingers. When instructed, subjects abducted the lateral surface of the index finger against a force transducer (LC1205-K020; A&D Mercury Pty Ltd, Australia) placed in-line with the distal interphalangeal joint. During precision grip, subjects opposed the index finger and thumb against a purpose built manipulandum that has been described previously [32]. The procedure to assess the MVC was identical for both index finger abduction and precision grip: subjects were required to produce maximum force for 3 s in several repetitions, separated by 30 s rest, until the maximal force of three trials were within a 10% margin. The largest force recorded during these trials was chosen as the subject's MVC. To optimize force production, feedback was displayed on a computer monitor placed at eye level in front of the subject, and verbal encouragement was provided by the experimenter.

Transcranial magnetic stimulation

TMS was applied to the left primary motor cortex using a figure-of-eight coil (external wing diameter 9 cm) with three Magstim 200 magnetic stimulators connected via two Bistim units (Magstim, Dyfed, UK). Within this setup, two stimulators were connected via