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Threshold tracking transcranial magnetic stimulation: Effects of age and gender on motor cortical function

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HIGHLIGHTS

- The impact of age and gender on cortical excitability was evaluated.
- Aging prolonged central latencies but exerted no significant effect on intracortical inhibition.
- Our results are valuable not only for normal physiology but also diagnostic studies.

ABSTRACT

Objective: Recently, the utility of threshold tracking paired-pulse transcranial magnetic stimulation (TTTMS), to measure changes in cortical excitabilitability, has been established for diagnostic purposes across a range of neurological diseases. However, the impact of healthy aging on the GABA-ergic intracortical inhibitory system remains unclear. To improve the clinical applicability, TTTMS was performed across an age spectrum.
Methods: TTTMS, single-pulse TMS and nerve conduction studies (NCS) were performed in 113 healthy subjects aged between 20 and 83 years (57 male and 56 female).
Results: Prolonged motor evoked potential (MEP) latency, increased central motor conduction time, decreased compound muscle action potential (CMAP) amplitude, prolonged F-wave latency and decreased neurophysiological index (NI), calculated from CMAP amplitude, latency and F-wave frequency, were observed as subjects aged. In contrast, short interval intracortical inhibition (SICI) and facilitation did not change. Compared to females, males exhibited a reduced SICI and NI along with longer MEP, CMAP with prolonged F-wave latencies. Multivariate analyses revealed similar results.
Conclusion: Utilizing clinically applicable TTTMS protocols, findings suggest that GABA mediated intracortical inhibition may be greater in females but does not significantly change with age.
Significance: These findings may better inform the interpretation of diagnostic TTTMS studies in the clinical setting.

1. Introduction

In clinical neurophysiological practice, electromyography and nerve conduction studies are commonly utilized to detect peripheral nerve dysfunction. In contrast, quantitative assessment of upper motor neuron dysfunction, using techniques such as transcranial magnetic stimulation (TMS), has proven difficult to validate in a clinical setting (de Carvalho, 2012). Furthermore, although identification of both upper and lower motor neuron signs remains critical for a diagnosis of amyotrophic lateral sclerosis (ALS) (Brooks et al., 2000), eliciting upper motor neuron signs can be difficult (Swash, 2012), particularly if there is coexistent lower motor neuron loss. Recently, threshold tracking paired-pulse TMS (TTTMS) techniques have been developed, that have identified underlying pathomechanisms in neurological diseases states (Vucic et al., 2006, 2010, 2011b, 2012, 2013; Vucic and Kiernan, 2008, 2013; Burrell et al., 2011; Huynh et al., 2013; Menon et al., 2015). In clinical practice, TTTMS differentiates ALS

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patients from mimic disorders with high sensitivity and specificity (Menon et al., 2015). Accordingly TTTMS techniques are being increasingly utilized in analyzing pathophysiology and may also prove to be of benefit in clinical diagnostic practice.

In addition to clinical utility, paired-pulse TMS techniques may non-invasively assess gamma-aminobutyric acid (GABA)-ergic inhibition, with short interval intracortical inhibition (SICI) and intracortical facilitation (ICF) acting as biomarkers of corticomotoneuronal function. To date, studies assessing the effect of age on cortical function and GABA-ergic inhibition in healthy subjects have revealed conflicting findings, with a full range of cortical excitability changes reported, from increased excitability (Peinemann et al., 2001; Heise et al., 2013; Opie and Semmler, 2014), through to unchanged excitability (Wassermann, 2002; Oliviero et al., 2006), and even decreased excitability documented in older subjects (Kossev et al., 2002; Smith et al., 2009; McGinley et al., 2010). Factors underlying these discordant findings remain to be elucidated, although may relate to different methodologies, including resting or active state measurements, the strength of conditioning stimulus, different recording muscles, coil orientation and relatively small cohort size (Opie et al., 2015; Sale et al., 2016). Separately, gender may also influence cortical excitability via modulation of GABA-ergic inhibitory interneurons (Kokate et al., 1994; Lan and Gee, 1994; Smith et al., 1999). Specifically, progesterone enhances the activity of the GABA-ergic system by increasing the $GABA_A$ receptor activity, and thereby influencing cortical excitability.

While the research and clinical utility of cortical excitability measurements have been increasingly recognized over recent years with the development of the TTTMS, the influences of age and gender on cortical function have not been assessed. As such, the present study utilized TTTMS, single pulse TMS, and nerve conduction studies in a large cohort of healthy subjects from across the adult age spectrum. The aim of this study was twofold: first to determine whether there existed age- and gender-related differences in SICI and ICF using TTTMS which might impact on clinical diagnostic use; and second to confirm alterations in single pulse TMS and nerve conduction parameters associated with healthy aging.

2. Methods

2.1. Subjects

Healthy participants from across an age spectrum were invited to participate in the present study provided there was no evidence of neurological abnormality, and that they were not prescribed medications with known nervous system effects. Participants with clinical symptoms or neurological findings diagnostic of carpal tunnel syndrome were excluded from the study. All subjects gave written informed consent to the procedures and the research was approved by the Human Research Ethics Committees of the South Eastern Sydney Local Health District and the Western Sydney Local Health District.

2.2. Cortical function assessed by transcranial magnetic stimulation

Paired-pulse TTTMS was undertaken using a 90 mm circular coil applied to the motor cortex, with currents generated by two magnetic stimulators connected via a BiStim 200^2 system (Magstim Co., Whitland, South West Wales, UK). The motor evoked potential (MEP) response was recorded over the abductor pollicis brevis (APB). Briefly, using the threshold tracking method, the amplitude of the MEP was set to a target value of 0.2 mV, and the changes in the intensity of the test stimulus required to generate this target MEP of 0.2 mV (±20%) were measured, preceded by subthreshold conditioning stimuli, using previously described protocols and as detailed below (Vucic and Kiernan, 2006; Vucic et al., 2006). These protocols are in current clinical and research use in the assessment of neurological disorders at our study centers. Resting motor threshold (RMT) was defined as the stimulus intensity required to maintain the target MEP (0.2 mV). Three stimuli of 150% RMT were delivered to measure the maximum MEP amplitude (mV), MEP onset latency (ms) and cortical silent period (CSP) duration. CSP duration was manually assessed from MEP onset to the return of EMG activity (Kimberley et al., 2009). The MEP amplitude was expressed as a percentage of the compound muscle action potential (CMAP) amplitude recorded following electrical stimulation MEP/CMAP ratio.

$$\text{MEP/CMAP ratio} = (\text{MEP amplitude (mV)}/\text{CMAP amplitude (mV)}) \times 100$$

Central motor conduction time (CMCT, ms) was calculated as in previous reports, using MEP latency, F-wave latency and distal motor latency (Claus, 1990). The CSP duration was measured from the beginning of MEP to return of EMG activity. SICI and ICF were measured according to previously defined protocols (Vucic and Kiernan, 2006). SICI was determined using subthreshold conditioning stimuli (70% RMT) at increasing sequential interstimulus intervals (ISIs; 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, and 7 ms) and ICF was measured at ISIs of 10, 15, 20, 25 and 30 ms. For each ISI, stimuli were delivered until two consecutive target MEPs (0.2 mV) were detected. SICI was measured as the increase in the test stimulus intensity required to evoke the target MEP 0.2 mV ± 20%. Similarly, facilitation was measured as the decrease in the conditioned test stimulus intensity required to maintain the same size target MEP 0.2 mV ± 20%. SICI or ICF were calculated as follows (Vucic et al., 2006):

$$\text{SICI or ICF} = (\text{Conditioned test stimulus intensity} - \text{RMT})/\text{RMT} \times 100$$

SICI was analyzed at ISI 1 ms, 2 ms, 3 ms, 3.5 ms and averaged (ISI 1–7 ms), and ICF was averaged (ISI 10–30 ms), as in previous studies (Vucic et al., 2006, 2010, 2011b, 2012, 2013; Vucic and Kiernan, 2008, 2013; Burrell et al., 2011; Huynh et al., 2013; Menon et al., 2015). ISI 1 ms and 3 ms were selected because there are two peaks of SICI identified at 1 ms and 3 ms in healthy subjects using these protocols (Fisher et al., 2002; Vucic et al., 2006). SICI at 2 and 3.5 ms were analyzed because SICI may be less contaminated by facilitation at these intervals (Peurala et al., 2008). These procedures were performed on a single side, as no differences due to laterality were identified in a previous study (Huynh et al., 2013). MEPs were recorded from the dominant hand (Right $N = 108$; Left $N = 5$).

2.3. Peripheral nerve conduction studies

In the same setting, the median nerve was stimulated electrically at the wrist using 5-mm Ag–AgCl surface electrodes. The CMAP was recorded from the APB and the CMAP onset latency and peak–peak amplitude were measured. Subsequently, F-wave latency and persistence were measured. The F-wave latency was determined as the minimal F-wave latency of 20 trials, and the F-wave frequency was calculated as the percentage of these 20 trials where an F-wave occurred. The neurophysiological index (NI), a useful marker to detect lower motor neuron loss, was calculated as an index of peripheral nerve function as previously reported, utilizing 3 nerve conduction parameters as per below (Swash and de Carvalho, 2004; Cheah et al., 2011).