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A meta-analysis of the effects of aging on motor cortex neurophysiology assessed by transcranial magnetic stimulation

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HIGHLIGHTS

- TMS measures of motor cortical excitation, inhibition and plasticity were assessed in young vs older adults.
- Age-related motor cortical hypo-excitability and a trending decrease in LTP-like plasticity observed.
- Older adults showed deficits in sensorimotor integration in comparison to young adults.

ABSTRACT

Objective: Transcranial magnetic stimulation (TMS) is a non-invasive tool used for studying cortical excitability and plasticity in the human brain. This review aims to quantitatively synthesize the literature on age-related differences in cortical excitability and plasticity, examined by TMS.
Methods: A literature search was conducted using MEDLINE, Embase, and PsycINFO from 1980 to December 2015. We extracted studies with healthy old (50–89 years) versus young (16–49 years) individuals that utilized the following TMS measures: resting motor threshold (RMT), short-interval cortical inhibition (SICI), short-latency afferent inhibition (SAI), cortical silent period (CSP), intracortical facilitation (ICF), and paired associative stimulation (PAS).
Results: We found a significant increase in RMT ($g = 0.414$, 95% confidence interval (CI) [0.284, 0.544], $p < 0.001$), a significant decrease in SAI ($g = 0.778$, 95% CI [0.478, 1.078], $p < 0.001$), and a trending decrease in LTP-like plasticity ($g = -0.528$, 95% CI [−1.157, 0.100] $p < 0.1$) with age.
Conclusions: Our findings suggest an age-dependent reduction in cortical excitability and sensorimotor integration within the human motor cortex.
Significance: Alterations in the ability to regulate cortical excitability, sensorimotor integration and plasticity may underlie several age-related motor deficits.

1. Introduction

By 2050 the number of adults aged 65 years and over is estimated to reach nearly 1.5 billion world-wide, representing 16% of the world's population (NIH, 2011). With a rapidly aging global population the economic, societal, and personal costs of neurodegenerative and neuropsychiatric diseases are expected to spike. This will present a significant burden to families, support workers, and health care providers. An enhanced understanding of the

Abbreviations: TMS, transcranial magnetic stimulation; GABA, gamma-aminobutyric acid; RMT, resting motor threshold; SICI, short-interval cortical inhibition; SAI, short-latency afferent inhibition; CSP, cortical silent period; ICF, intracortical facilitation; PAS, paired associative stimulation; LTP, long-term potentiation; LTD, long-term depression; NMDA, N-methyl-D-aspartate; EMG, electromyography; ISI, interstimulus interval; CI, confidence interval; SD, standard deviation; CNS, central nervous system; PNS, peripheral nervous system.

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impact of aging on cortical functioning may help provide more insight into age-related illnesses.

Normal aging is characterized by neurophysiological and neuroanatomical changes of the brain. These changes are thought to underlie the decline in sensorimotor control and function that can accompany advancing age. An inability to modulate cortical excitability is suggested to underlie several motor deficits that healthy older adults may experience in daily life such as the deterioration of fine motor skills (Calautti et al., 2001), impaired coordination skills (Swinnen et al., 1998; Serrien et al., 2000; Heuninckx et al., 2004), and a decline in reaction times (Bedard et al., 2002).

The primary inhibitory neurotransmitter in the brain is gamma-aminobutyric acid (GABA). GABA plays a central role in mediating cortical excitability (DeFelipe et al., 1986; Schieber and Hibbard, 1993). Cortical pyramidal cell activity is modulated by excitatory inputs, excitatory post-synaptic potentials (EPSPs), and inhibitory inputs, inhibitory post-synaptic potentials (IPSPs) (Krnjevic, 1997). The inhibitory inputs are produced by GABAergic interneurons that terminate on these cells (Krnjevic, 1997). The selective attenuation of cortical pyramidal activity by inhibitory GABA interneurons is termed cortical inhibition (Daskalakis et al., 2007). Recent studies suggest a direct correlation between a decreased ability to modulate cortical inhibition and motor retardation in healthy older adults (Fujiyama et al., 2012b; Heise et al., 2013; Levin et al., 2014).

GABAergic neurotransmission is also central to the induction and maintenance of neuroplasticity (Daskalakis et al., 2007). The brain's ability to adapt to internal and external stimuli is dependent on neuroplasticity; a process by which the brain reorganizes and generates new neural pathways. The induction and maintenance of neuroplasticity is contingent upon activity-dependent alterations in synaptic strength (van Mier et al., 1998; Daskalakis et al., 2008). The most extensively studied forms of neural plasticity are: long-term potentiation (LTP) and long-term depression (LTD). LTP, the strengthening of neuronal connections in highly activated pathways, increases the likelihood of synaptic firing to additional stimuli; conversely LTD, the weakening of poorly activated pathways, reduces the likelihood of synaptic firing (Hebb, 1949). Age-related deficits in LTP-like plasticity may underlie motor learning deficits observed in healthy older adults.

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation tool used to assess cortical excitability and plasticity, *in vivo* (Rossini et al., 2015). Two TMS paradigms used to index cortical inhibition are: short-interval cortical inhibition (SICI) (Kujirai et al., 1993) and cortical silent period (CSP) (Cantello et al., 1992). SICI is a paired-pulse TMS paradigm that requires the paired delivery of two TMS stimuli, whereby a subthreshold conditioning stimulus precedes a suprathreshold test stimulus by 1–4 ms (Kujirai et al., 1993).

In contrast, CSP is a single-pulse paradigm that requires the delivery of a suprathreshold TMS pulse to the contralateral motor cortex during voluntary contraction of the target muscle (Cantello et al., 1992). The suprathreshold TMS pulse evokes a motor-evoked potential (MEP) followed by a period of suppressed electromyography (EMG) activity. The duration of the silent period is measured from the onset of the MEP to the return of EMG activity (Cantello et al., 1992).

An extensive body of literature suggests SICI and CSP represent $GABA_A$ and $GABA_B$ inhibitory neurotransmission respectively. For instance, the pharmacological profiles of SICI and CSP differ greatly. Benzodiazepines (e.g. lorazepam) act as positive allosteric modulators at $GABA_A$ receptors and reliably facilitate SICI. Conversely baclofen, a $GABA_B$ receptor agonist, prolongs CSP duration (Paulus et al., 2008). In addition to differing pharmacological profiles, $GABA_A$ receptor-mediated IPSP peaks at 20 ms while the $GABA_B$ receptor-mediated IPSP peaks at 150–200 ms; this corresponds to the time course of SICI and CSP duration (McCormick, 1989; Davies et al., 1990; Sanger et al., 2001).

As well as cortical inhibition, TMS protocols are used to index cortical excitability. Cortical excitability can be assessed using the following TMS paradigms: resting motor threshold (RMT) and intracortical facilitation (ICF). The RMT measures general neuronal membrane excitability and is defined as the minimum intensity that evokes an MEP > 50 μV in a muscle at rest in 5 out of 10 trials (Rossini et al., 1994). ICF is a paired-pulse TMS paradigm that involves the paired delivery of a subthreshold conditioning stimulus preceding a suprathreshold test stimulus by 10–25 ms, resulting in MEP facilitation (Kujirai et al., 1993; Nakamura et al., 1997). Pharmacological studies suggest ICF indexes N-methyl-D-aspartate (NMDA) glutamate-mediated excitatory neurotransmission (Paulus et al., 2008).

Paired associative stimulation (PAS) is a TMS paradigm used to induce LTP and LTD-like cortical plasticity. PAS involves pairing repetitive, low-frequency peripheral median nerve stimulation (MNS) with TMS stimulation to the motor cortex. To induce potentiation of cortico-motor excitability (LTP-like plasticity) the MNS must precede the TMS stimulus by an interstimulus interval (ISI) of 25 ms; to induce depression (LTD-like plasticity) the MNS must precede the TMS stimulus by 10 ms (Stefan et al., 2000; Weise et al., 2013).

Glutamatergic NMDA receptors represent the molecular basis of LTP and LTD (Miyamoto, 2006; Zorumski and Izumi, 2012). PAS-induced facilitation of cortical excitability is critically dependent on NMDA receptor function. For example, blockade of NMDA receptors prevents PAS-induced facilitation of cortico-motor excitability (Ridding and Ziemann, 2010). Therefore, PAS-induced cortical plasticity, LTP, and LTD are thought to rely on shared neuronal mechanisms (Luscher and Malenka, 2012). This review will quantitatively assess the effect of age on PAS-induced LTP-like plasticity.

The impact of age on sensorimotor integration can be evaluated using the TMS paradigm short-latency afferent inhibition (SAI). SAI requires median nerve stimulation paired with a single TMS pulse to the motor cortex. If the ISI is 20 ms, the afferent nerve conditioning produces a marked decrease in EMG activity from the single TMS pulse (Classen et al., 2000; Tokimura et al., 2000). At the biological level, SAI is thought to primarily index cholinergic transmission. For example, scopolamine, a muscarinic acetylcholine receptor antagonist, selectively reduces the SAI cortical response in healthy subjects (Di Lazzaro et al., 2000).

A limited number of TMS studies have examined the impact of healthy aging on cortical excitability and plasticity in healthy older adults. The trends in the current literature remain inconclusive and a synthesis of findings is lacking. Thus, we undertook a meta-analysis to quantitatively synthesize the literature on TMS measures of cortical excitability and plasticity in healthy older adults compared to younger adults – refer to Table 1 for an overview of the included TMS studies.

2. Methods

2.1. Data sources

A literature search was conducted using MEDLINE, Embase, and PsycINFO from 1980 through December 2015. This search was supported by a hand search of bibliographies. Please refer to the Supplementary File for a description of the exact terms used in the literature search.