Neuropsychologia 102 (2017) 190–196

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Cortical excitability and neuropsychological functioning in healthy adults

Lauren B. Bolden[a,b,*], Joseph C. Griffis[a,b], Sandipan Pati[b,c], Jerzy P. Szaflarski[b,c]

[a] Department of Psychology, University of Alabama at Birmingham, Birmingham, AL, USA
[b] Department of Neurology, University of Alabama at Birmingham, Birmingham, AL, USA
[c] UAB Epilepsy Center, University of Alabama at Birmingham, Birmingham, AL, USA

ARTICLE INFO

Keywords:
TMS
Hyperexcitability
$GABA_B$
Intracortical inhibition
Attention
Mood state

ABSTRACT

Evidence from clinical populations, such as epilepsy and attention deficit/hyperactivity disorder, suggests a relationship between hyperexcitability and cognitive impairment, but this relationship has not been demonstrated in healthy individuals. Here, we investigate the relationship between cortical excitability and cognitive functioning in healthy adults. Single- and paired-pulse TMS was applied to 20 healthy adults to measure cortical excitability and long-interval intracortical inhibition (LICI). A neuropsychological battery was administered to assess aspects of attention, executive function, and mood. Participants with primarily excitatory responses to the LICI paradigm performed worse on a composite measure of attention and reported more negative mood states than participants with primarily inhibitory responses.

Thus, differences in attention and mood among healthy adults are related to differences in cortical excitability as measured by LICI. This is consistent with a role for $GABA_B$ inhibitory circuits in regulating attention and mood, and suggests that individual variability in these domains may reflect variability in cortical excitability. This study demonstrates preliminary evidence that increased cortical excitability is associated with poorer cognition and mood in healthy adults. These findings provide new insight into the presence of cognitive dysfunction in several patient populations with hyperexcitability and support the development of neurostimulation interventions for clinical use.

1. Introduction

The human brain is comprised of hierarchical networks of excitatory and inhibitory neurons that enable complex cognitive processes such as attention and emotion (Park and Friston, 2013). Within this network, at the level of microcircuit, there are interconnected excitatory glutamatergic pyramidal cells and inhibitory GABAergic interneurons. Maintaining balance between inhibition and excitation is critical for accurate and effective communication across synapses, which is the basis for every aspect of behavior (Badawy et al., 2012b). There is evidence that the alteration of this dynamic equilibrium plays a role in cognitive and behavioral dysfunctions that occur in various neuro-psychiatric diseases. Hyperexcitability, or an abnormal increase in excitatory neurotransmission, may be produced by either the suppression of inhibitory networks or excessive activity in excitatory networks (i.e. decreased inhibition or increased facilitation) (Wu et al., 2014). While the mechanisms underlying hyperexcitability vary amongst different disease populations, motor cortical hyperexcitability is found in patients with various neurological and neuropsychiatric disorders such as epilepsy, autism spectrum disorders, amyotrophic lateral sclerosis, Tourette syndrome, attention-deficit/hyperactivity disorder (ADHD), and schizophrenia, among others (Badawy et al., 2012b; Bunse et al., 2014; Hoegl et al., 2012; Radhu et al., 2012; Strube et al., 2014).

In addition to an increase in cortical excitability, several of the above-mentioned populations demonstrate deficits in cognition, with an overrepresentation of frontal lobe cognitive dysfunction. More specifically, these populations exhibit dysfunction in the executive and attention domains, suggesting the possibility of a relationship between hyperexcitability and cognitive difficulties (Badawy et al., 2012a; Devinsky et al., 1997; Harris et al., 1995; Kerns et al., 2008). For example, epilepsy is a disease associated with neuronal network hyperexcitability that can lead to local and/or generalized network dysfunction (Hermann and Seidenberg, 1995). Epilepsy patients commonly exhibit executive functioning and attention deficits, even when their epilepsy onset zone is outside of frontal cortex; it is generally believed that the location of the ictal discharge onset and its spread is responsible for the specific cognitive impairments observed in these patients (Badawy et al., 2012a). The nociferous cortex hypothesis posits that executive system dysfunction in patients with temporal lobe epilepsy is caused by epileptogenic cortex adversely affecting the extra-

* Correspondence to: Department of Neurology and UABEC, University of Alabama at Birmingham, 312 Civitan International Research Center, 1719 6th Avenue South, Birmingham, AL 35294-0021, USA.
E-mail address: lbolden@uab.edu (L.B. Bolden).

http://dx.doi.org/10.1016/j.neuropsychologia.2017.06.028
Received 1 February 2016; Received in revised form 22 May 2017; Accepted 22 June 2017
Available online 23 June 2017
0028-3932/

temporal regions that mediate these abilities (Hermann and Seidenberg, 1995). Similarly, patients with ADHD show increased cortical excitability and behavioral/attention problems that are ameliorated by treatment with methylphenidate, providing support for the notion that frontal lobe hyperexcitability may be a primary factor underlying cognitive dysfunction in domains such as attention (Schneider et al., 2011). Thus, while the relationship between hyperexcitability and cognitive dysfunction is well recognized in several disease populations, the relationship between cortical excitability and cognitive performance in healthy individuals is not clear and we were unable to identify specific studies addressing this issue. The characterization of this relationship in healthy individuals is important for understanding the pathologies underlying cognitive symptoms in clinical populations and for developing effective treatment strategies.

Neurostimulation techniques such as transcranial magnetic stimulation (TMS) can alter cortical excitability and impact cognitive performance in healthy and disease states (Bolden et al., 2015; Hwang et al., 2010; Klimesch et al., 2003; Liao et al., 2015; Shah et al., 2013). TMS is a non-invasive brain stimulation technique that can be used as diagnostic tool to measure various aspects of cortical excitability, including resting motor threshold (RMT) (Kobayashi and Pascual-Leone, 2003). Obtaining an accurate RMT is the methodological basis for evaluating other aspects of cortical excitability, including intracortical inhibition (ICI), which has been specifically shown to differ between healthy and patient populations such as epilepsy (Badawy et al., 2010b; Hasan et al., 2013). To assess ICI, a form of TMS called paired-pulse TMS (ppTMS) is used to apply pairs of stimulation that are separated by varying interstimulus intervals (ISIs) to the motor cortex (Kujirai et al., 1993; Valls-Sole et al., 1992). Different ppTMS paradigms are used to evaluate two types of ICI: short-interval ICI (SICI) and long-interval ICI (LICI). SICI and LICI are thought to reflect the activity of $GABA_A$-mediated (Boroojerdi, 2002) and $GABA_B$-mediated circuits (Mott and Lewis, 1994; Ziemann et al., 1996), respectively. Compared to healthy individuals, patients with epilepsy exhibit decreased inhibition in both SICI and LICI, although the most striking differences are exhibited on LICI recovery curves (Badawy et al., 2013b). In fact, patients with epilepsy actually show excitatory responses on most if not all LICI ISIs, depending on the type of epilepsy (Badawy et al., 2007; Brodtmann et al., 1999; Valzania et al., 1999). A decreased inhibitory response to the LICI paradigm can be used as an outcome measure of hyperexcitability, and is interpreted as most likely reflecting dysfunction of intracortical $GABA_B$ circuits.

Evidence from clinical populations, such as epilepsy and ADHD, suggests a relationship between hyperexcitability and cognitive impairment, particularly in frontal lobe cognitive domains (e.g. executive function and attention). However, there is a gap in the literature regarding inter-individual differences in the cortical excitability of healthy individuals and how these differences relate to cognitive functioning. Before the relationship between cortical excitability and cognition can be assessed in clinical populations, its relationship in healthy participants must first be established. Therefore, the aim of the proposed study was to investigate the relationship between cortical excitability and cognitive functioning in healthy adults. Single and ppTMS was used to measure various aspects of cortical excitability, including RMT and LICI. A neuropsychological battery assessed executive functioning and attention skills and a self-report questionnaire was used to assess mood state. Based on the findings from hyperexcitable clinical populations, we hypothesized that participants with increased cortical excitability would have poorer outcomes on tests of cognitive performance and mood state than participants with lower levels of cortical excitability.

2. Methods

2.1. Participants

The data utilized in this study were obtained from 24 healthy adults. Exclusion criteria for this study included: diagnosis of a neurological disorder, no high school diploma, age less than 19 or more than 45 years, contraindication to TMS (e.g., metal plate in skull), and positive pregnancy test in woman of childbearing age. Of the 24 participants recruited, 3 were excluded from analyses due to equipment error, and one participant was excluded due to a violation of the age exclusion criteria. Twenty healthy adults (12 females) were included in the subsequent analyses. Participants ranged in age from 20 to 44 years (M = 31.10 years, SD = 7.51), 70% were Caucasian, and the mean years of education was 15.90 (SD = 3.77). The University of Alabama at Birmingham Institutional Review Board approved this study, and all participants provided written informed consent prior to enrollment.

2.2. Procedure

After signing IRB-approved consent, participants completed a demographics questionnaire, the Edinburgh Handedness Inventory (Oldfield, 1971), and a pregnancy test when applicable. Single and paired-pulse TMS was then applied to each participant. Following TMS, 45–60 min of neuropsychological and psychological testing was performed. A brief neurological exam was conducted by a board certified/eligible neurologist to ensure participant readiness and safety to leave the visit. The total protocol duration was approximately 2.5 h. All participants received a follow-up phone call 4 weeks following assessment.

2.3. Transcranial magnetic stimulation

All single and paired-pulse TMS protocols were performed with a Magstim 200® stimulator connected through a Bistim® module to a 70 mm figure-8 coil (Magstim Co., Wales, UK). During TMS, participants were seated in a comfortable chair that was partially reclined, with both arms fully supported by armrests, and both legs supported by individual leg rests. Surface electromyography (EMG) electrodes were placed over the first dorsal interosseous (FDI) muscle of the participant's left hand to record motor evoked potentials (MEPs). In order to locate the vertex, subjects wore a latex swim cap on which the midpoints between the preauricular points, and between the nasion to inion lines, were drawn (Jaspers, 1958). Lines and markings were then drawn on the cap to identify the position 5 cm lateral from the vertex, known as the average motor “hot spot” location (Rossini et al., 1994); The “hot spot” indicates the location on the scalp that produces the largest MEPs from the target muscle when the subject is stimulated at rest. Stimulations were then administered to this location and surrounding areas systematically until each individual's “hot spot” was identified. A frameless stereotaxic system (Brainsight, Rogue Inc., Montreal, Canada) provided online feedback throughout the TMS session to ensure the location of stimulation at the “hot spot” was held constant. The handheld TMS coil was positioned tangentially over the right hemisphere of all participants, regardless of handedness, with the handle pointing posteriorly at all times.

2.3.1. Resting motor threshold

RMT was determined in the right motor cortex while participants were at rest. Stimulation intensity began at 35% of the stimulator output and increased in 2% increments until each individual's “hot spot” was located. Note that TMS intensities reflect a percentage of the maximum stimulator output. Subsequent changes in intensity occurred in 1% increments to determine RMT, or the minimum stimulus intensity required to produce a MEP between 50 and 100 μV in at least 5 out of 10 consecutive stimulations when the FDI muscle was at rest (Rossini