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Review

Aging and motor inhibition: A converging perspective provided by brain stimulation and imaging approaches

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ABSTRACT

The ability to inhibit actions, one of the hallmarks of human motor control, appears to decline with advancing age. Evidence for a link between changes in inhibitory functions and poor motor performance in healthy older adults has recently become available with transcranial magnetic stimulation (TMS). Overall, these studies indicate that the capacity to modulate intracortical (ICI) and interhemispheric (IHI) inhibition is preserved in high-performing older individuals. In contrast, older individuals exhibiting motor slowing and a declined ability to coordinate movement appear to show a reduced capability to modulate GABA-mediated inhibitory processes. As a decline in the integrity of the GABA-ergic inhibitory processes may emerge due to age-related loss of white and gray matter, a promising direction for future research would be to correlate individual differences in structural and/or functional integrity of principal brain networks with observed changes in inhibitory processes within cortico-cortical, interhemispheric, and/or corticospinal pathways. Finally, we underscore the possible links between reduced inhibitory functions and age-related changes in brain activation patterns.

Contents

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1. Introduction

1.1. Overview and aims

Normal aging is characterized by changes in the structural and functional integrity of the brain. These changes are marked, at the behavioral level, by progressive deterioration of motor and cognitive functions (Fling and Seidler, 2012a; Heuninckx et al., 2008; Langan et al., 2010; Nielson et al., 2002; O'Sullivan et al., 2001; see reviews, Seidler et al., 2010; Swinnen et al., 2011; Turner and Spreng, 2012). Some of the neurodegenerative processes in healthy aging, including changes in structural (e.g., Inano et al., 2011) and biochemical (e.g., Gao et al., 2013) properties of the brain, are argued to affect cortical inhibitory functions. Age-related deficits in the ability to control cerebral inhibition may explain many behavioral declines that healthy older adults experience in daily life, such as longer reaction times (e.g., Bedard et al., 2002; Jordan and Rabbitt, 1977), impaired coordination skills (e.g., Heuninckx et al., 2004; Serrien et al., 2000; Swinnen et al., 1998) and deterioration of fine motor functions (e.g., Calautti et al., 2001). There is also some evidence that inhibition at both corticospinal (Oliviero et al., 2006; Peinemann et al., 2001; Sale and Semmler, 2005) and spinal (Kido et al., 2004) levels of the central nervous system (CNS) decreases with advancing age. With the increasing use of neuroimaging techniques, a systems level approach has been developed which links age-related deteriorations in behavioral performance with changes in the functional and structural properties of brain networks that control motor inhibition (e.g., Coxon et al., 2009; Jackson et al., 2012).

At the cortical level, motor inhibition is largely mediated via activation of gamma-aminobutyric acid (GABA) receptors. GABA is a principal inhibitory neurotransmitter in the brain tissue of mammalians with a rich structural diversity of receptors and a dense representation of GABA-ergic interneurons in the neocortex (e.g., Blatow et al., 2005). Deficiencies or abnormalities in GABA-ergic activity have been documented in many cognitive and/or movement disorders, particularly in those diseases where excess or undesired movements emerge such as dystonia (Di Lazzaro et al., 2009) and epilepsy (Fedi et al., 2008) (see review, Hallett, 2011; Ramamoorthi and Lin, 2011). Importantly, the activity of cortical GABA-ergic inhibitory interneurons can be monitored in vivo with transcranial magnetic stimulation (TMS) (e.g., Siebner et al., 1998; Ziemann et al., 1996b; see review, Reis et al., 2008). This makes TMS a powerful tool to investigate the neurophysiological mechanisms associated with age-related changes in the regulation of GABA-ergic inhibitory function. The main aim of the present review is to provide, specifically, an overview of age-related changes in GABA-ergic mediated intracortical and interhemispheric inhibitory processes (as monitored with TMS), with particular reference to their impact on declines in motor performance with advancing age. A question of interest in this context is to what extent declines of GABA-ergic inhibitory functions are operating as underlying mechanisms for motor performance declines in the absence of overt pathology.

Functional neuroimaging techniques (e.g., functional magnetic resonance imaging, fMRI) and TMS are expected to generate complementary information on age-related changes in functional communication between brain regions: fMRI underscores the neuroanatomical boundaries of the brain regions involved in a task, whereas TMS is used to explore the presence and strength of inhibitory and excitatory projections between those brain regions and M1 more directly. Likewise, TMS and structural neuroimaging may be used to link age-related changes in the ability to modulate inhibition with differences in white matter microstructural organization and gray matter volume of brain regions that project into M1. Studies combining TMS and diffusion tensor imaging (DTI) in young adults have already indicated that inhibitory functions are strongly affected by differences in the brain's structural properties (Buch et al., 2010; Fling et al., 2011b; Neubert and Klein, 2010; Wahl et al., 2007). Similarly, there is also evidence to suggest that age differences in interhemispheric connectivity affect functional brain activity (Langan et al., 2010). In the past, TMS and neuroimaging techniques have been used to study aging independently from each other with some exceptions (Fling and Seidler, 2012a; Lanza et al., 2013; McGregor et al., 2013, 2011; Talelli et al., 2008a). The secondary aim of this review is, therefore, to further advance our current understanding of the mechanisms which underlie age-related changes in GABA-ergic inhibitory functions, associated with age-differences in motor performance, specifically focusing on findings from neuroimaging studies that reported age-differences in the brain's function (e.g., Heuninckx et al., 2008; Nielson et al., 2002) or structure (e.g., Coxon et al., 2009; O'Sullivan et al., 2001) that predict declines in motor functions.

1.2. Transcranial magnetic stimulation (TMS)

For the sake of clarity, here we provide a brief overview of the relevant TMS techniques which are central neurophysiological techniques in the current review. The physiological effect of TMS over the primary motor cortex (M1) can be quantified by measuring the motor-evoked potential (MEP) obtained from surface electromyographic (EMG) activity in the target muscles (Hallett, 2000; Rossini et al., 2010; Rothwell, 1997). The MEP amplitude obtained with TMS reflects the net effect of excitatory and inhibitory inputs to the motor cortex pyramidal cells. GABA-ergic inhibitory processes can be explored through the application of various TMS techniques. For example, the paired-pulse TMS paradigm (Kujirai et al., 1993), in which two separate pulses with a short (2–3 ms) interstimulus interval (ISI) are delivered to the motor cortex through the same TMS coil at rest, provides a measure for excitability of inhibitory interneurons within M1 (intracortical inhibition, ICI): the first sub-threshold (conditioning) stimulus is applied to recruit intracortical inhibitory interneurons which reduce the MEP amplitude produced by the second (supra-threshold) test stimulus. This phenomenon is referred to as short-interval intracortical inhibition (SICI). Evidence for the involvement of $GABA_A$-ergic inhibition in the generation of SICIs came from a pharmacological study by Ziemann et al. (1996a) which observed increased SICI by the ingestion of lorazepam, a positive modulator of the $GABA_A$ receptor. Another form of cortical inhibition induced with a paired-pulse TMS paradigm is long interval intracortical inhibition (LICI), in which two superthreshold stimuli of equal intensities applied with a long ISI (50–200 ms) (Valls-Sole et al., 1992). Evidence from a pharmacological study suggests that LICIs are mediated by $GABA_B$ receptors (Werhahn et al., 1999).

Paired-pulse paradigms that combine peripheral afferent nerve stimulation with TMS (e.g., Tokimura et al., 2000) may be used to monitor activity of non-GABA-ergic inhibitory pathways;