

**AGE RELATED CHANGES IN
CORTICOMOTOR AND INTRACORTICAL
EXCITABILITY IN MEN**

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DOCTOR OF PHILOSOPHY



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ABSTRACT

Age-related motor deficits manifest in many ways including slowing of movement, increased unwanted movements and difficulties learning new motor tasks. Despite this decline in “motor” brain function, the physiological mechanisms underlying these changes are largely unknown. One brain region innately involved in the control of voluntary movement is the human primary motor cortex. The mono-synaptic corticospinal output cells projecting from the primary motor cortex to the periphery, as well as the intra-cortical excitatory and inhibitory interneurons that synapse onto the corticospinal output neurons are important for facilitating voluntary movement. Whether or not the efficacy of these neuronal pathways is altered with advancing age has not previously been investigated in depth. Therefore, the overall aim of the studies described in this thesis was to characterise the changes in corticomotor and intracortical inhibitory network excitability that occur with ageing in otherwise neurologically healthy human males.

Previous studies have provided some limited evidence of age-related changes in corticomotor excitability in humans. However interpretation of these data is complicated by the fact that all the studies were performed on both men and women; there is increasing evidence that post-menopausal loss of neuroactive estrogen in women alters cortical excitability and may have confounded the findings of previous studies where sex-specific changes have not been considered. Therefore in chapter 2 I investigated whether corticomotor excitability differed when a group of ageing men was compared with a group of young adult men. I found that corticomotor excitability was not influenced by age in either hemisphere, suggesting that in men aged less than 75 years, the efficacy of the corticomotor projection is preserved when examined in the absence of voluntary activation.

The excitability of the corticospinal output neurons is highly influenced by the net balance of excitatory and inhibitory inputs onto them by cortical interneurons. In the absence of voluntary activation, the excitability of the intracortical inhibitory networks is high. This so-called intracortical inhibition is principally mediated by the neurotransmitter gamma-aminobutyric acid (GABA) acting at different

classes of GABA receptors, probably on different neuronal populations. The two main GABA receptor types mediating motor intracortical inhibition are GABA receptor type A (GABA_A) and GABA receptor type B (GABA_B). Studies using paired pulse transcranial magnetic stimulation (TMS) techniques to examine these different types of inhibition in the motor cortex have shown that inhibition mediated by GABA_A receptors tends to occur at short interstimulus intervals (1 – 5 ms) and is therefore commonly termed short-interval intracortical inhibition (SICI). Conversely, motor cortex inhibition mediated by GABA_B receptors tends to occur at longer interstimulus intervals (100 – 200 ms) and is therefore commonly termed long-interval intracortical inhibition (LICI). There have been few investigations of the possible influence of ageing on SICI and the results have been equivocal with no consensus on whether SICI is increased, decreased or unchanged by ageing. Only one previous study has examined the effects of ageing on LICI in males and females, and reported it to be increased. Therefore, I investigated the influence of ageing on GABA_A (Chapter 3) and GABA_B (Chapter 4) mediated motor cortex inhibition when ageing and young adult men were compared. In chapter 3, I show that SICI is unchanged by ageing in men. I also present evidence of how the findings of previous studies are likely to have been confounded by several methodological aspects, particularly the TMS parameters used to study SICI, specifically the intensity of the conditioning stimulus. In chapter 4, I present evidence that suggests that LICI is increased in ageing men when compared with young adult men. While statistically significant, the magnitude of this increase in GABA_B mediated inhibition was very small and required a relatively large sample size to elucidate. However, the functional influence of this increase in LICI with age was not investigated, and whether or not this change is of sufficient magnitude to be behaviourally relevant is yet to be confirmed.

On balance, the studies described in Chapters 2-4 inclusive provide little evidence of major changes in either corticomotor excitability or intracortical inhibitory network efficacy with age. However, these three studies were all performed in the absence of voluntary activation of the motor cortex or corticospinal tract, i.e. “at rest”. It may be that ageing alters the ability to modulate the excitability of these networks (e.g. by afferent input from the periphery) rather than their absolute level of excitability. Indeed, afferent

input has been shown to be a powerful modulator of intracortical inhibition, particularly SICI, and this interaction appears to be important for motor control during an ongoing movement or preparation for movement. Therefore, in chapter 5 I describe a study where SICI was compared in young and ageing men under two conditions; firstly in the absence of voluntary activation and, secondly, in the presence of cutaneous afferent stimulation of the skin overlying a finger controlled by a muscle in whose cortical representation SICI was being examined. In several previous studies of young adults by others, this afferent input has been shown to reduce the amount of motor cortex inhibition subsequently evoked. Confirming the findings reported in Chapter 3, when assessed in the absence of voluntary activation or afferent input, SICI did not differ when young and old men were compared. However, with appropriately timed afferent input the subsequent degree of inhibition evoked was only reduced in the young men, but not in the old men. Using a process of elimination, I concluded that this reduced modulation of inhibition in the old men was most likely due to altered cortical sensorimotor integration of afferent input with age, as the peripheral afferent volley to the cortex appeared preserved and the level of SICI in the absence of afferent input was not different between the two age groups. It is probably not possible to confirm the exact cortical site and mechanism underlying this alteration *in vivo* in humans. However, my findings suggest that it is likely to involve neural projections (originating either within the motor cortex, or from elsewhere) that probably synapse with motor cortex inhibitory interneurons and are responsible for the modulation of their activity *via* afferent input from the periphery.

In summary, the studies described in this thesis contribute two main general findings. Firstly, when investigated without voluntary activation and/or significant afferent input, the efficacy of the corticospinal tract and the main inhibitory interneurons acting upon corticospinal output cells, is not altered by ageing in otherwise neurologically healthy men. However, the “at rest” condition may mask ageing-related changes in the neural mechanisms that modulate corticomotor excitability and GABAergic intracortical inhibition. Therefore, future studies probing the neural mechanisms underlying ageing-related changes in human motor cortex function should not only be sex-specific, but also need to be undertaken under

conditions that include input to the motor cortex from the periphery (i.e. afferent input) or other brain regions involved in voluntary motor system activation.

DECLARATION

I Ashleigh Elizabeth Smith certify that this work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief contains no material previously published or written by another person except where due reference has been made in the text.

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ABBREVIATIONS

ADM	abductor digiti minimi muscle
AMT	active motor threshold
ANCOVA	analysis of co-variance
ANOVA	analysis of variance
APB	abductor pollicis brevis muscle
AUC	area under the curve
COV	co-efficient of variation
CS	conditioning stimulus
CSICI	conditioned short-interval intracortical inhibition
D-wave	direct wave
EMG	electromyography/ electromyograms
EPSP	excitatory post-synaptic potential
FAMAS	Florey Adelaide Male Ageing Study
FDI	first dorsal interosseous muscle
GABA	γ -amino butyric acid
GABA _A	γ -amino butyric acid receptor type A
GABA _B	γ -amino butyric acid receptor type B
H-reflex	Hoffmann reflex
ICF	intracortical facilitation
I-wave	indirect wave
LICI	long-interval intracortical inhibition
LQ	laterality quotient (derived from Edinburgh handedness inventory)
M1	primary motor cortex
MEP	motor evoked potential
MEP _{max}	maximum MEP amplitude

ms	milliseconds
MVC	maximum voluntary contraction
pRMT	predicted resting motor threshold
RMT	resting motor threshold
SD	standard deviation
SICI	short-interval intracortical inhibition
SLOPE ₁₀	slope of the input output curve at 10% of MEP _{max}
SLOPE ₂₅	slope of the input output curve at 25% of MEP _{max}
SLOPE _{max}	slope of the input output curve at MEP max
SO	stimulator output
TES	transcranial electrical stimulation
TMS	transcranial magnetic stimulation
WMH	white matter hyperintensity/hyperintensities

GENERAL INTRODUCTION

The monosynaptic cortico-motor-neuronal component of the corticospinal system plays an essential role in the control of human movement, and in particular, the control of the intrinsic hand muscles responsible for independent finger movements. In this thesis, the term corticomotor excitability rather than corticospinal excitability is used when interpreting results based on the analysis of motor evoked potentials (MEPs) recorded with surface electromyography, since the corticomotor component of the corticospinal tract is responsible for the MEP, not just the corticospinal tract. Despite a documented decline in “motor” function with “normal” ageing, the underlying physiological mechanisms are unknown. At the level of the primary motor cortex, discharge of pyramidal cells is mediated by a fine balance between inhibitory and excitatory inputs from horizontal interneurons with which they synapse. Disruptions to voluntary movement have been characterised in diseased patient groups when this fine balance between inhibition and facilitation is disturbed (Ridding et al. 1995a; Ridding et al. 1995b; Brown et al. 1996). For example, Parkinson’s disease, focal hand dystonia’s and even some psychiatric disorders are characterised by abnormal levels of corticomotor excitability and inhibition. However, it is still unknown if similar abnormal levels of corticomotor excitability and inhibition occur in the “healthy” ageing motor system. Therefore, the broad aims of the studies described in this thesis were to characterise changes in human corticomotor and intracortical inhibitory pathways that occur with “healthy” ageing.

Previous research demonstrated a rightward shift of corticospinal stimulus response curves occurs with increased age (Pitcher et al. 2003). However, it was suggested that this shift may only be evident in women, and be driven by age-related hormonal changes, rather than by ageing *per se*. Therefore, the study described in chapter two aimed to determine if these age-related changes in corticomotor excitability are evident in men only. Corticospinal stimulus response curves were constructed for the primary motor cortices of both hemispheres of young and old male subjects, and compared.

The functionally relevant GABA_A mediated cortico-cortical inhibitory circuits have variously been shown to be increased (Kossev et al. 2002), decreased (Peinemann et al. 2001) or not changed with age (Wassermann 2002; Oliviero et al. 2006; Cirillo et al. 2010). However, there is evidence that GABA_A mediated short-interval intracortical inhibition (SICI) in the motor cortex is less variable if conditioning intensities are set relative to active motor threshold (AMT) (Orth et al. 2003). Therefore, in the studies described in chapter 3, I investigated the effect of age on these SICI networks (Kujirai et al. 1993). SICI and facilitation (ICF) was initially investigated in old compared to young men using previously described conditioning and test stimulus parameters. Secondly, the effect of setting CS intensity relative to AMT was examined with age using SICI curves.

Most of the previous work relating to the intracortical inhibitory networks and ageing is focussed on SICI, with few studies investigating the age-related changes in the GABA_B mediated long-interval intracortical inhibitory circuits (LICI) (McGinley et al. 2010). Only one study, conducted in both males and females has reported LICI is increased with age (McGinley et al. 2010). However, this study only investigated LICI at a single interstimulus interval, at a single conditioning intensity and only in the non-dominant hemisphere motor cortex. In young subjects LICI has been shown to be asymmetrical with a lower threshold and faster progression in the dominant compared to the non-dominant hemisphere (Hammond and Garvey 2006). Therefore, the age-related changes may be missed if only investigated at a single conditioning intensity in the non-dominant hemisphere. Experiments detailed in chapter 4 aimed to determine if threshold for LICI, inhibition, or saturation of LICI, is changed with increased age in men, in both the dominant or non-dominant primary motor cortices.

Aside from age-related changes in the excitability of the inhibitory networks, it is possible that ageing is associated with a reduction in the ability to modulate them. It has been previously demonstrated, in young individuals, that precisely timed afferent input can reduce SICI measured with TMS in a topographically specific manner (Ridding and Rothwell 1999; Ridding et al. 2005). This ability to

modulate SICI appears to be important, not only for the control of ongoing movement, but also for facilitating neuroplasticity, since neuroplasticity is enhanced when SICI is reduced (Ziemann et al. 1998b; Ziemann et al. 2001). Evidence from comparing young and old participants, demonstrates an age-related decline in the control of fine movements and a reduced capacity for neuroplasticity occurs, although whether this is due to a decline in modulation of SICI networks is unknown (Cirillo et al. 2010; Todd et al. 2010). Therefore, in chapter 5, I aimed to determine if precisely timed afferent input can modulate the SICI circuits similarly with increased age.