

**INVESTIGATING INTRACORTICAL
INHIBITORY MECHANISMS CONTRIBUTING
TO AGE-RELATED DEFICITS IN MOTOR
FUNCTION**

A thesis submitted for the Degree of

DOCTOR OF PHILOSOPHY



THE UNIVERSITY
of **ADELAIDE**

by

George Opie

B. Health Sciences (Hons)

Discipline of Physiology

School of Medical Sciences

Adelaide, Australia

July, 2015

Abstract.....	vi
Declaration	viii
Acknowledgements	ix
1. Literature Review	1
<i>1.1. Neural control of movement.....</i>	<i>2</i>
1.1.1. Human motor cortex.....	2
1.1.2. Intracortical inhibition and γ -aminobutyric acid (GABA)	5
1.1.3. Descending pathways in the control of movement.....	7
1.1.4. Hand function and Grip-Lift tasks.....	9
<i>1.2. Brain stimulation and Transcranial Magnetic Stimulation</i>	<i>11</i>
1.2.1. Development of non-invasive brain stimulation (NIBS) techniques	11
1.2.2. Transcranial Magnetic Stimulation (TMS)	12
1.2.3. Single-pulse TMS.....	15
1.2.4. Paired-pulse TMS	17
1.2.5. Triple-pulse TMS	21
<i>1.3. Healthy ageing, intracortical inhibition & TMS.....</i>	<i>22</i>
1.3.1. Age-related changes in form and function	23
1.3.2. Age-related changes in GABA.....	27
<i>1.4. Further characterising age-related changes in ICI.....</i>	<i>34</i>
1.4.1. Corticospinal input-output properties.....	34
1.4.2. Activity-related cortical disinhibition.....	36
1.4.3. Task-related cortical disinhibition.....	37
1.4.4. Interactions between inhibitory circuits	39
1.4.5. Movement phase.....	40
<i>1.5. Summary.....</i>	<i>42</i>
2. Modulation of short- and long-interval intracortical inhibition with increasing	
motor evoked potential amplitude in a human hand muscle	46

2.1. <i>Abstract</i>	46
2.2. <i>Introduction</i>	47
2.3. <i>Methods</i>	49
2.3.1. Experimental arrangement.....	49
2.3.2. Experimental Procedures	50
2.3.3. Data Analysis.....	52
2.3.4. Statistical Analysis	53
2.4. <i>Results</i>	53
2.4.1. Influence of test TMS intensity on SICI and LICI	54
2.4.2. Influence of test MEP amplitude on SICI and LICI.....	58
2.4.3. Influence of test MEP amplitude on SICI and LICI (Experimental Series 2).....	60
2.4.4. Linear regression	62
2.5. <i>Discussion</i>	64
2.5.1. Factors influencing SICI and LICI.....	65
2.5.2. Influence of normalised test MEP amplitude on SICI.....	67
2.5.3. Influence of normalised test MEP amplitude on LICI	68
2.5.4. Test TMS intensity vs. normalised test MEP amplitude	69
2.5.5. Physiological Significance	70
3. Age-related differences in short- and long-interval intracortical inhibition in a	
 human hand muscle	75
3.1. <i>Abstract</i>	75
3.2. <i>Introduction</i>	76
3.3. <i>Materials and Methods</i>	77
3.3.1. Experimental arrangement.....	77
3.3.2. Experimental Procedures	78
3.3.3. Data Analysis.....	80
3.3.4. Statistical Analysis	80
3.4. <i>Results</i>	81

3.4.1. Influence of test TMS intensity on the test alone MEP in young and old subjects.....	82
3.4.2. Influence of age on SICI and LICI.....	83
3.4.3. Influence of test TMS intensity and test MEP amplitude on age-related changes in SICI.....	84
3.4.4. Influence of test TMS intensity and test MEP amplitude on age-related changes in LICI.....	87
3.4.5. Grip-lift performance and linear regression.....	90
3.5. <i>Discussion</i>	92
3.5.1. Advancing age influences SICI in active but not resting muscle.....	92
3.5.2. Advancing age influences LICI in resting and active muscle.....	94
4. Task-related changes in intracortical inhibition assessed with paired- and triple-pulse transcranial magnetic stimulation.....	99
4.1. <i>Abstract</i>	99
4.2. <i>Introduction</i>	100
4.3. <i>Methods</i>	102
4.3.1. Experimental arrangement.....	102
4.3.2. Experimental Procedures.....	104
4.3.3. Data Analysis.....	108
4.3.4. Statistical Analysis.....	109
4.4. <i>Results</i>	110
4.4.1. Test MEP characteristics.....	110
4.4.2. Intracortical inhibition.....	113
4.5. <i>Discussion</i>	120
4.5.1. Task-related variations in postsynaptic intracortical inhibition (SICI and LICI).....	120
4.5.2. Task-related variations in presynaptic motor cortex inhibition (LICI-SICI interactions).....	122

4.5.3. Timing-dependent variations in intracortical inhibition.....	124
5. Age-related differences in pre- and post-synaptic motor cortex inhibition are task dependent.....	128
5.1. <i>Abstract</i>	128
5.2. <i>Introduction</i>	129
5.3. <i>Materials and methods</i>	131
5.3.1. Experimental arrangement.....	131
5.3.2. Experimental Procedures.....	133
5.3.3. Data Analysis.....	136
5.3.4. Statistical Analysis.....	137
5.4. <i>Results</i>	138
5.4.1. Test MEP characteristics.....	139
5.4.2. Short-interval intracortical inhibition.....	141
5.4.3. Long-interval intracortical inhibition.....	141
5.4.4. SICI in the presence of LICI.....	143
5.4.5. Linear regression.....	149
5.5. <i>Discussion</i>	151
5.5.1. Effects of age on short-interval intracortical inhibition.....	151
5.5.2. Effects of age on long-interval intracortical inhibition.....	153
5.5.3. Effects of age and task on the interaction between LICI and SICI.....	154
6. Intracortical inhibition is modulated during slow shortening and lengthening contractions in young and old adults.....	160
6.1. <i>Abstract</i>	160
6.2. <i>Introduction</i>	161
6.3. <i>Methods</i>	163
6.3.1. Ethical approval.....	163
6.3.2. Subjects.....	163

6.3.3. Experimental arrangement.....	163
6.3.4. Experimental Procedures.....	164
6.3.5. Data Analysis.....	168
6.3.6. Statistical analysis	169
<i>6.4. Results</i>	<i>169</i>
6.4.1. Intracortical inhibition.....	171
6.4.2. Motor output during anisometric movements	178
6.4.3. Linear regression	178
<i>6.5. Discussion</i>	<i>180</i>
6.5.1. SICI is modulated by movement in young and old adults.....	181
6.5.2. LICI is modulated during lengthening contractions in old but not young subjects.....	182
6.5.3. Old adults demonstrate greater cortical disinhibition during anisometric contractions	184
6.5.4. Movement-related changes in inhibition appear unrelated to motor performance	185
7. General Discussion.....	187
<i>7.1. Corticospinal input/output properties and ageing.....</i>	<i>188</i>
<i>7.2. Inhibitory interactions, motor task and ageing.....</i>	<i>189</i>
<i>7.3. Movement and ageing</i>	<i>193</i>
<i>7.4. Concluding remarks.....</i>	<i>196</i>
8. Appendices.....	197
<i>8.1. Appendix I: Publications arising from thesis.....</i>	<i>197</i>
<i>8.2. Appendix II: Presentations and abstracts arising from thesis.....</i>	<i>198</i>
9. Bibliography	200

Abstract

Within the primary motor cortex, the activity of local GABAergic interneurons is important in the generation of graded and specific patterns of muscle activation. This intracortical inhibitory tone is therefore an essential aspect of fine motor function. For this reason, abnormal inhibitory tone has often been investigated as a potential contributing factor in situations of altered motor control, such as is seen in healthy older adults. However, despite extensive investigation, studies assessing age-related changes in intracortical inhibition have produced inconsistent findings. The purpose of this thesis was to characterise how the ageing process affects intracortical inhibition, and to identify functional consequences of age-related changes in inhibitory tone. This was achieved by applying single-, paired- and triple-pulse transcranial magnetic stimulation (TMS) in young and old adults under a number of different conditions.

In Chapters 2 and 3, the effects of age-related changes in corticospinal input/output properties on comparisons of short- (SICI) and long-interval intracortical inhibition (LICI) between young and old subjects was assessed. This study found that differences in corticospinal recruitment mainly affect age-related comparisons of inhibition during voluntary activation, with comparisons during relaxation mostly unaffected. Furthermore, significant reductions in post-synaptic GABA_B-mediated inhibition were also observed in old adults.

Subsequently, by investigating interactions between LICI and SICI, Chapters 4 and 5 assessed if these changes in GABA_B-mediated inhibition involved the activity of pre-synaptic receptors. Furthermore, the modulation of SICI, LICI and LICI-SICI interactions during simple (abduction) and complex (precision grip) motor tasks was also compared between young and old subjects. These studies found age-related changes in both pre- and post-

synaptic GABA_B-mediated inhibition, as well as a reduced task-dependent modulation of intracortical inhibition in old adults.

In the final experimental chapter (Chapter 6), the modulation of SICI and LICI in young and old adults was investigated during slow shortening and lengthening contractions of a hand muscle controlling the index finger, the performance of which is known to be impaired by ageing. While both groups showed disinhibition during movement, this was significantly greater in old adults for both SICI and LICI. Furthermore, disinhibition of SICI varied between contraction phases for young (but not old) adults, whereas disinhibition of LICI varied between contraction phases for old (but not young) adults. These findings suggest that old adults modulate GABAergic inhibition differently during movement. However, if and how this altered inhibitory modulation contributes to age-related motor deficits during movement remains unclear.

This thesis has provided novel insights into the effects of age on GABAergic intracortical inhibition within primary motor cortex, some of which may contribute to the motor deficiencies that are commonly observed in healthy older adults. Furthermore, our findings have established several lines of investigation for future research, including some with the potential to produce positive clinical outcomes in older individuals. However, our results also demonstrate the need for an increased understanding of the functional relationship between TMS measures of inhibitory neurotransmission and motor output.

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, 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. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

I give consent to this copy of my thesis when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968.

The author acknowledges that copyright of published works contained within this thesis resides with the copyright holder(s) of those works.

I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

Signed..

Date.....12/6/15.....

Acknowledgements

First and foremost I would like to thank my supervisors for their invaluable support throughout the duration of my PhD; to my primary supervisor Associate Professor John Semmler, for his constant patience, guidance and support in all aspects of this thesis, and to my secondary supervisor Associate Professor Michael Ridding, for his prompt feedback and methodological assistance. This thesis would not have been possible without the influence of such excellent supervision.

Secondly, I would like to thank all of the individuals who volunteered to participate in my experiments, particularly those that were willing to come back in time after time. Many of the experiments were long and sometimes tedious for these subjects, and I greatly appreciate their assistance.

Last, but in no way least, I would like to thank my family; to my mum, dad, brother and grandparents, Queenie and Geoff, for their support, encouragement, and interest during the course of all my studies. I would particularly like to thank Tegan for always putting up with me during the more frustrating parts of my PhD, and always helping me to recognise and celebrate accomplishments along the way, however small or large.