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

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by

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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

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