TOWARDS ESTABLISHING LONG-LASTING NEUROPLASTIC CHANGE IN THE HUMAN PRIMARY MOTOR CORTEX

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ABSTRACT

Neuroplasticity is critical for learning, memory, and recovery of lost function following neurological insult. Whilst non-invasive brain stimulation techniques capable of inducing these neuroplastic changes within the human cortex could be therapeutically beneficial for a range of neurological and psychiatric conditions, the short duration, instability, and variability of induced effects limits their therapeutic potential. This thesis has investigated approaches to enhance the duration, stability, and consistency of the neuroplastic response to non-invasive brain stimulation protocols applied to the human primary motor cortex.

The neuroplasticity-inducing paradigm employed throughout this thesis was continuous theta burst stimulation (cTBS), a repetitive transcranial magnetic stimulation (rTMS) paradigm shown to suppress human motor cortical excitability. Studies in animals have shown the repeated, spaced application of stimulation protocols to prolong the duration of experimentally-induced synaptic plasticity. Therefore, Chapter 2 examined whether the spaced application of repeated cTBS protocols enhanced the lifetime of induced neuroplastic effects within the human primary motor cortex. Whilst the neuroplastic response to a single cTBS protocol was minimal, paired cTBS protocols spaced 10 min apart induced a strong suppression of motor cortical excitability that lasted for at least 2 h. A further set of experiments were performed to determine the possible contribution of the inhibitory motor networks to this enhanced neuroplastic response (Chapter 3). Although paired cTBS reduced the excitability of $GABA_A$-mediated inhibitory motor networks, this effect was only modest. Also, paired cTBS had no effect on $GABA_B$-mediated inhibition. These findings suggest that the enhanced neuroplastic response to

paired cTBS was likely the result of greater suppression within excitatory motor networks rather than a facilitation of inhibitory motor networks.

In addition to prolonging the duration of experimentally-induced synaptic plasticity, the repeated application of stimulation protocols has also been shown to consolidate these plastic changes in animal models, making them resistant to reversal by subsequent behaviourally-relevant physiological activity. In Chapter 4, I investigated whether the neuroplastic response to paired cTBS was similarly resistant to reversal by behavioural engagement of the stimulated motor regions. Whilst a voluntary activation of the targeted hand muscles reversed the neuroplastic response to a single cTBS protocol, the long-lasting neuroplastic response to paired cTBS was resistant to the same reversal effects. These results suggest that, similar to animal models of synaptic plasticity, the neuroplasticity induced by cTBS may be consolidated when repeated protocols are applied in a spaced manner.

Although Chapters 2, 3, and 4 show a long-lasting and robust response to repeated cTBS protocols, the neuroplastic response to a single cTBS was highly variable between subjects. This may have been due, in part, to non-optimal stimulation characteristics. Therefore, the experiments described in Chapter 5 compared the efficacy of the standard cTBS paradigm ($cTBS_{std}$) to that of a slightly modified variant ($cTBS_{mod}$). Compared to $cTBS_{std}$, $cTBS_{mod}$-induced neuroplasticity was highly consistent between subjects, suggesting that this may be the more effective neuroplasticity-inducing paradigm.

This thesis demonstrates approaches for inducing long-lasting neuroplastic changes within the human primary motor cortex. These findings have important implications for the therapeutic application of rTMS.

DECLARATION

I, Mitchell Ryan Goldsworthy, 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. In addition, I certify that no part of this work will, in the future, be used in a submission 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.

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SIGNED…….. DATE……

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AIMS & GENERAL INTRODUCTION

Neuronal networks within the human brain undergo constant reorganizational changes throughout life in response to different experiences, a phenomenon termed neuroplasticity. Neuroplasticity is an essential property of the human nervous system and is critically important for an array of normal brain processes. The human motor system has a remarkable capacity for undergoing this neuroplastic change, enabling us to learn and continually refine the accuracy and efficacy of a large range of complex movements. Likewise, this motor cortical plasticity is important for the recovery of motor skills lost due to neurological injury. For instance, in the chronic stages following stroke, much of the recovery of motor function is likely to occur as a result of neuroplasticity. Accordingly, a central focus of neuroscientific research has been to develop therapeutic strategies which beneficially enhance this neuroplastic change. It is hoped that these strategies may someday be used either on their own or in conjunction with conventional rehabilitative therapies to drive neuroplasticity within the affected brain region and promote recovery of lost function. One such strategy exists in the form of non-invasive brain stimulation.

There is much promise of non-invasive brain stimulation techniques to be used as therapeutic agents in treating a range of neurological and psychiatric conditions. However, given the short lifetime and instability of their induced effects within the human motor system, as well as the high variability of individual responses, the implementation of these techniques in a clinical setting is, at present, far from established. Thus, the studies described in this thesis have aimed to optimise the

application of these non-invasive brain stimulation protocols such that they produce longer lasting and more robust neuroplastic effects within the human motor system.

Unlike the long-lasting synaptic plasticity induced experimentally in animal models using trains of electrical stimulation, the neuroplasticity induced within the human primary motor cortex using repetitive transcranial magnetic stimulation (rTMS) has a very short lifetime that rarely persists for more than 1 h. This discrepancy may be due to differences in the approaches used to apply stimulation trains: whereas rTMS is applied as a single train in humans, the stimulation protocols used in animals are often applied repeatedly in a spaced manner.

Following a review of the literature in Chapter 1, the first three experimental chapters of this thesis will examine the possible benefits of applying repeated trains of an rTMS paradigm (continuous theta burst stimulation; cTBS) to the human primary motor cortex. Specifically, I will examine the lifetime of the induced neuroplastic changes (Chapter 2), the motor networks at which these changes are likely to occur (Chapter 3), and also the stability of these changes in the presence of behaviourally-relevant physiological activity (Chapter 4). The final experimental chapter will shift focus to the stimulation parameters used for cTBS, with the aim of optimising a single cTBS application such that the induced neuroplastic changes in the human primary motor cortex are less variable between individuals (Chapter 5). This thesis will close with a discussion of the main findings, with a focus on the implications of this research for the therapeutic application of non-invasive brain stimulation.