# EXPERIMENTALLY INDUCED CORTICAL PLASTICITY: NEUROPHYSIOLOGICAL AND FUNCTIONAL CORRELATES IN HEALTH AND DISEASE

*A thesis submitted for the Degree of*

## DOCTOR OF PHILOSOPHY


*by*

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## Abstract

Neuroplasticity provides the basis for many of our most fundamental processes including learning, memory and the recovery of function following injury. This thesis is concerned with the neurophysiological and functional correlates of sensorimotor neuroplasticity in the healthy and focal dystonic populations.

My initial experiments were conducted to determine the functional correlates of neuroplasticity induced in the primary motor (M1) and primary sensory (S1) cortices during a grip lift task. In healthy subjects these experiments further quantified the role of M1 in the anticipatory control of grip force scaling and demonstrated a role for S1 in triggering subsequent phases of the motor plan. My second series of experiments served to extend these findings by examining the functional correlates of neuroplasticity induced in the supplementary motor area (SMA). This study provided evidence for the role of left SMA in the control of grip force scaling and a role for left and right SMA in the synchronization of grip force and load force during the grip-lift synergy.

Afferent input is known to be a powerful driver of cortical reorganisation. In particular, the timing and pattern of afferent input is thought to be crucial to the induction of plastic change. In healthy subjects, I examined the neurophysiological effects of applying "associative" (synchronous) and "non-associative" (asynchronous) patterns of afferent input to the motor points or digits of the hand. I observed an increase in the volume and area of the cortical representation of stimulated muscles when associative stimulation was applied over the motor points of two hand muscles. This pattern of stimulation also caused the centres of gravity of the stimulated muscles to move closer together, mimicking the maladaptive changes seen in

focal hand dystonia. Non-associative stimulation and stimulation applied to the digits did not produce such an effect.

Task-specific focal dystonia is characterised by excessive representational plasticity resulting in cortical representations which are significantly larger, and demonstrate greater overlap, than those seen in healthy individuals. These changes are thought to be driven, in part, by repetitive movement patterns which promote associative patterns of afferent input over an extended time period. On the basis of this knowledge, I applied non-associative stimulation to the hand muscles of dystonic subjects. Following this intervention, I noted a contraction of representational maps and a separation in the centres of gravity of the stimulated muscles. These neurophysiological changes were accompanied by improvements on a cyclic drawing task.

This thesis demonstrates the functional correlates of neuroplasticity in M1, S1 and SMA during object manipulation using a precision grasp. These findings further extend our knowledge on the mechanisms underlying effective grasp control and assist us in the development of future rehabilitation protocols for neurological conditions involving grasp dysfunction. In addition, this thesis is the first to demonstrate an improvement in both neurophysiological and functional measures in focal dystonia following a period of non-associative afferent stimulation. These results open up exciting new avenues for the development of effective treatment protocols in those with focal hand dystonia.

## Declaration

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 to Siobhan Schabrun 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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## Chapter 2: Role of M1 and S1 in precision grasping



## Chapter 3: Role of SMA in precision grasping



## Chapter 4: Correlated afferent input and M1 representations



## Chapter 5: Normalising representations in FHD

## Aims and general introduction

In recent years our understanding of the human central nervous system has advanced considerably. Where the structure and function of the adult central nervous system was once thought to be static, it is now clear that this system retains the ability to restructure and reorganise throughout life. This property, known as plasticity, is of significant importance in learning and memory, and is likely to play a key role in recovery of motor function following injury.

Reorganisation of the human cortex has been demonstrated using a number of experimental paradigms. However, evidence for a concomitant and related functional effect is limited. Investigation of the functional effects associated with cortical reorganisation is of critical importance if novel and effective rehabilitation strategies are to be developed for those with neurological conditions.

The neurophysiological correlates of cortical plasticity may be measured using transcranial magnetic stimulation (TMS). Using the principles of electromagnetic induction, TMS triggers neuronal depolarisation and the propagation of a descending volley of action potentials in the corticospinal tract. This volley activates motor neurons and induces a transient electromyographical (EMG) response in the target muscle known as a motor evoked potential (MEP). Changes in MEP amplitude reflect changes in the excitability of the corticospinal projection to the target muscle and are used as a marker of plasticity induction.
TMS may also be applied repetitively (rTMS) as a tool to induce cortical reorganisation. This approach can be used to induce a temporary “virtual lesion” that interrupts activity in a specific cortical region or, by altering the frequency, intensity or direction of the stimulation,

rTMS can be used to transiently alter synaptic strength. The functional correlates of rTMS-induced plasticity may then be determined.

In my first series of experiments I used the technique of rTMS to induce plasticity in the primary motor (M1) and primary sensory (S1) cortices of healthy subjects performing a grip-lift task. The grip-lift task has been shown to be a sensitive, objective measure of hand dexterity in both healthy subjects and in those with neurological conditions. As one limitation of previous studies has been the use of functional measures with insufficient sensitivity to detect subtle changes in performance, a grip-lift apparatus was considered the most appropriate tool for this study. The results of this study, detailed in Chapter 2, demonstrate functional effects which are highly correlated with the induction of plasticity in M1 and S1. Specifically, rTMS applied over M1 disrupted the ability to accurately anticipate the grip force needed to lift a small object, while rTMS applied over S1 hampered the ability to initiate subsequent phases of the motor plan.

A second series of experiments extended these findings by applying rTMS over the supplementary motor area (SMA) using a similar paradigm and the same grip-lift task. In healthy subjects, application of rTMS led to changes in the temporal and dynamic aspects of the grip-lift task and these changes demonstrated a hemispheric lateralisation. Disruption to left SMA produced a significant increase in the grip force needed to lift an object regardless of the hand used in the task. Conversely, disruption to right SMA reduced the synchronisation of the grip force to the object load force. These experiments are described in Chapter 3.

In animal models, temporally coupled afferent inputs have been shown to induce cortical reorganisation characterised by expansion and greater overlap of representational zones. In human subjects, paradigms utilising this “associative input” have also been shown to induce plastic change. However, it is unclear whether plasticity induced by associative afferent input

in human subjects is characterised by representational changes analogous to those seen in animal studies. This question was addressed in Chapter 4. I used a period of associative afferent stimulation applied to two hand muscles or two digits in healthy individuals and contrasted these findings with a period of non-associative afferent stimulation. Subjects receiving associative stimulation to the motor points demonstrated cortical representations which were larger in both area and volume and centred closer together. These changes were not present following associative stimulation applied to the digits or following non-associative stimulation.

A number of neurological conditions are thought to involve abnormal cortical plasticity. In particular, task-specific focal hand dystonia (FHD) is a debilitating neurological condition characterised by aberrant and maladaptive cortical plasticity. Previous studies have shown that cortical representations in FHD are significantly larger and demonstrate greater overlap than those in healthy individuals. While the exact mechanism is unclear, it appears that a genetic predisposition coupled with repeated exposure to associative afferent inputs may trigger maladaptive cortical reorganisation. Based on this, the experiments described in Chapter 5 tested the hypothesis that non-associative stimulation applied to the motor points of affected hand muscles would promote normalisation of cortical representations and alleviate symptoms in FHD. All subjects performed a grip-lift and a handwriting task before receiving 1 hour of non-associative stimulation. A decrease in the volume and area of cortical representations, and a separation in the centres of gravity for the stimulated muscles, was observed. These changes were correlated with a functional improvement in the variability of cyclic drawing, suggesting that the induction of plasticity using a non-associative stimulation paradigm may be an exciting avenue for the development of novel and effective treatment strategies in FHD.