FACTORS INFLUENCING THE INDUCTION OF NEUROPLASTIC CHANGES IN HUMAN MOTOR CORTEX

A thesis submitted for the Degree of

DOCTOR OF PHILOSOPHY

by

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Abstract

The human primary motor cortex (M1) undergoes structural and functional change throughout life by a process known as neuroplasticity. Techniques which artificially induce neuroplastic changes are seen as potential adjunct therapies for neurological conditions reliant on neuroplasticity for recovery of function. Unfortunately, the reported improvements in function when these techniques have been used in combination with regular rehabilitation have so far been inconsistent. One reason attributed to this is the large variability in effectiveness of these techniques in inducing neuroplastic change. This thesis has investigated factors influencing the effectiveness and reproducibility of neuroplasticity induction in human M1 using several experimental paradigms.

The effectiveness and reproducibility of inducing neuroplasticity in human M1 using two variants of a paired associative stimulation (PAS) protocol was investigated in the first set of experiments (Chapter 2). Both protocols repeatedly paired a peripheral electrical stimulus to the median nerve of the left wrist with single-pulse transcranial magnetic stimulation (TMS) delivered 25 ms later to the contralateral M1. Neuroplastic changes were quantified by comparing the amplitude of the muscle evoked potential (MEP) recorded in abductor pollicis brevis (APB) muscle by suprathreshold TMS prior to and following PAS. With both protocols, neuroplasticity induction was more effective, and the responses across sessions more reproducible, if the experiments were performed in the afternoon compared to the morning.

Subsequent experiments confirmed the time of day modulation of PAS-induced neuroplasticity by repeatedly testing twenty-five subjects on two separate occasions,

once in the morning (8 am), and once in the evening (8 pm) (Chapter 3). Time of day was also shown to modulate GABAergic inhibition in M1. In a further set of experiments, a double-blind, placebo-controlled study demonstrated that artificially elevated circulating cortisol levels (with a single oral dose of hydrocortisone) inhibits PAS-induced neuroplasticity in the evening (8 pm), indicating that the time of day modulation of neuroplasticity induction with PAS is due, at least in part, to differences in circulating cortisol levels (Chapter 3).

The cortical circuits that are modulated by PAS have also been shown to be important in motor learning. Therefore, the final set of experiments, described in Chapter 4, investigated whether motor-training-related changes in motor performance (and cortical excitability) following a ballistic motor training task are also modulated by time of day. Twenty-two subjects repeatedly abducted their left thumb with maximal acceleration for thirty minutes during two experimental sessions (morning (8 am) and evening (8 pm)) on separate occasions. Motor training improved motor performance, and increased cortical excitability, however these changes were independent of time of day. It may be that the motor training task and/or outcome measures used were not sufficiently sensitive to detect a subtle time of day effect of motor training on motor performance. Alternatively, the normally functioning motor system may be able to compensate for changes in cortical excitability to maintain optimal motor performance.

These findings have important implications for therapies reliant on neuroplasticity for recovery of function, and indicate that rehabilitation may be most effective when circulating cortisol levels are low.

Declaration

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Sale MV, Ridding MC, Nordstrom MA. Factors influencing the magnitude and reproducibility of corticomotor excitability changes induced by paired associative stimulation. Exp Brain Res 2007;181:615-626.

Sale MV, Ridding MC, Nordstrom MA. Cortisol inhibits neuroplasticity induction in human motor cortex. J Neurosci 2008;28:8285-8293.

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List of figures

List of tables

Aims and general introduction

The human nervous system reorganises the strength of connections between neurons throughout adult life. This reorganisation is termed neuroplasticity, and is an important process associated with learning, memory and recovery from neurological insult. In recent years, several experimental techniques have been developed to artificially induce neuroplastic change in human cortex. Ultimately, it is hoped that these techniques will aid in promoting recovery from various neurological insults such as stroke.

One problem associated with these techniques is the large variability in effectiveness for inducing neuroplastic change. My initial study for this thesis, detailed in Chapter 2, sought to identify and understand the factors contributing to this variability. Two variants of a "paired associative stimulation" (PAS) protocol were used to induce plastic change in human motor cortex. The protocols differed in terms of frequency of stimulation and duration of the intervention. A range of neurophysiological and experimental variables were assessed to determine whether they influenced the extent of neuroplasticity induction by PAS. Subjects were randomly divided into the two PAS protocol groups and each subject was tested with the same protocol on three separate occasions, with each session at least one week apart. None of the neurophysiological variables examined reliably predicted an individual's response to the intervention. However, with both PAS protocols the induction of neuroplastic change was more effective, and more reproducible, for experiments conducted in the afternoon compared with the morning.

Since different subjects participated in the morning and afternoon experiments, my second set of experiments, detailed in Chapter 3, sought to directly test the hypothesis that time of day influenced neuroplasticity induction in human motor cortex. Subjects were assessed on two separate occasions, separated by at least one week. One session was in the morning (8 am), the other in the evening (8 pm), with the order of the sessions randomised. Salivary cortisol concentration was also measured before and after PAS. Cortisol release is under circadian control, and cortisol is known to inhibit learning and memory. These experiments demonstrated that time of day affects neuroplasticity induction with PAS, with significant neuroplasticity induction observed in evening experiments, but not in the morning. Salivary cortisol levels were greater in the morning than the evening, however, there was no significant relationship between the amount of neuroplasticity induced and salivary cortisol concentration in this study.

A third double-blind, placebo-controlled study was conducted to investigate more conclusively whether cortisol levels influence neuroplasticity induction. This study is also presented in Chapter 3. Subjects attended two experimental sessions at 8 pm (when endogenous cortisol levels are low), separated by at least one week. Prior to receiving PAS, subjects received either a single oral dose of hydrocortisone (which is metabolised to cortisol) or a placebo. Salivary cortisol levels were higher, and neuroplasticity induction by PAS was less effective when subjects were given oral hydrocortisone. This experiment provided strong evidence that neuroplasticity induction in human motor cortex is, at least in part, modulated by circulating levels of cortisol.

PAS is believed to induce neuroplastic change by mechanisms that are known to be important in motor learning. Chapter 4 details the fourth set of experiments which

aimed to determine whether there was a functional correlate for the time of day effect on neuroplasticity induction revealed by PAS. Subjects performed a ballistic thumb abduction motor training task on two separate occasions, in the morning (8 am) and evening (8 pm), separated by at least one week. The order of the sessions was randomised. The motor training task improved motor performance (as measured by maximum thumb acceleration) and also increased cortical excitability (assessed by TMS), but the extent of performance improvement following training was not dependent upon time of day. It may have been that the motor training task was not sufficiently sensitive to detect a subtle time-of-day modulation of motor performance following motor training, or that the normally functioning motor system is able to compensate for changes in cortical excitability to maintain motor output.

These studies demonstrate that the induction of neuroplasticity in human M1 using PAS is dependent on time of day. Neuroplasticity induction is more effective, and the reproducibility of the induced effects is greater, if experiments are performed in the evening. This effect is, at least to some extent, modulated by circulating cortisol levels. A functional correlate for the time-of-day modulation of neuroplasticity induction has not been found - motor performance changes induced with a repetitive ballistic thumb training task are not modulated by time of day. These findings have important implications for therapies reliant on neuroplasticity for recovery of function, and indicate that most effective rehabilitation may occur when circulating cortisol levels are low.