Somatosensory electrical stimulation produces motor learning and synaptic plasticity
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GENERAL INTRODUCTION
1. GENERAL INTRODUCTION

Successful acquisition and execution of motor skills require an intact motor but also high functioning sensory system. Cutaneous and proprioceptive stimuli provide feedback to the central nervous system via peripheral receptors and are essential to accurately perform activities of daily living, such as reaching and grasping movements [1]. Theoretical models verified by computational simulations predict the involvement of the sensory system in human motor function [2]. Such theoretical predictions are strengthened by clinical data showing that movement quality is reduced in macaques with an ablated sensory cortex [3] and humans with a damaged sensory system, such as spinal cord patients [4,5]. In addition, the magnitude of sensory function preservation after a stroke is positively associated with motor function and potential for motor recovery [6]. Together, these studies demonstrate a relationship between sensory and motor function that can be exploited in the rehabilitation of neurological patients suffering from motor dysfunctions who are unable to perform voluntary contractions to (re)learn motor skills.

1.1 SOMATOSENSORY ELECTRICAL STIMULATION INCREASES MOTOR PERFORMANCE

The idea that peripheral sensory stimulation can benefit patients with disorders affecting the central nervous system has been around for over three decades [7]. Indeed, enhancing sensory input using weak peripheral stimulation in the form of somatosensory electrical stimulation (SES), in this thesis defined as low-intensity (i.e., below motor threshold) electrical stimulation of peripheral nerves that excites cutaneous and proprioceptive afferents, improved functional motor performance in stroke patients [8,9]. Such effects appear to be spatially specific because SES to the paretic arm, but not to the paretic leg, immediately increased arm motor function in stroke patients [9]. In addition to the immediate effects, SES-induced increases in motor performance can outlast the period of stimulation up to one month [8], and there are indications that such effects may be transferable to the non-stimulated limb [10]. These studies highlight the clinical applicability of SES by showing its immediate effects on skill acquisition and its delayed effects on skill consolidation, defined as the offline enhancement or stabilization of motor memories [11]. However, the effects of SES have been only demonstrated in stroke patients and the mechanisms through which SES operates are fundamentally unclear. Mechanistic knowledge obtained in a healthy population could increase the efficacy of SES protocols in a clinical setting. The present thesis therefore focuses on the effects of SES on skill learning in healthy young adults and in addition aims to identify the mechanisms through which SES increases motor function by examining neurophysiological processes involved in motor learning using transcranial magnetic stimulation (TMS) and electroencephalography (EEG).
1.2 NEUROPHYSIOLOGICAL MECHANISMS UNDERLYING SES-INDUCED IMPROVEMENTS IN MOTOR PERFORMANCE

At least part of the improvements in motor performance after SES can be attributed to adaptations in the central nervous system. With the development of EEG in 1929 by Hans Berger and TMS in 1985 by Anthony Barker [12], it became possible to study brain activity and excitability non-invasively. Based on fundamental neuroscientific stepping-stones in the form of models of synaptic plasticity developed by Donald Hebb that are presented in his book ‘Organization of Behavior’ [13] and empirical evidence in mammals for this concept by means of long-term potentiation [14], EEG and TMS have increasingly been used to study the adaptability of synaptic connectivity in response to motor learning and sensory stimulation in the past 20 years [15-17].

It has become clear that the sensory and motor system interact at the segmental level through spinal interneurons that integrate sensory inputs and motor outputs [18]. At the cortical level, axons interconnecting the somatosensory cortex and the primary motor cortex (M1) were identified in rodents [19] and humans [20]. Such connections represent a neuroanatomical basis for SES-induced plasticity of the central nervous system that is evidenced by electrophysiological and imaging studies that revealed elevated excitability and activity levels in the contralateral M1, supplementary motor area, dorsolateral premotor area, posterior parietal cortex, primary sensory cortex, ipsilateral cerebellum, and bilateral secondary sensory cortex following SES [21-29]. Afferent sensory volleys from the upper extremity modify M1 most likely through corticocortical connections that link the M1 with the primary sensory cortex, secondary sensory cortex, and sensorimotor parietal cortex [20]. Direct evidence that SES modifies M1 comes from TMS studies that showed that SES increases the excitability of corticospinal pyramidal neurons in M1 [30,31]. These data point to use-dependent adaptations in synaptic plasticity after passive SES that are similar to synaptic plasticity after active motor practice, thereby giving rise to the idea that SES-induced increases in motor performance are mediated by cortical plasticity. However, such predictions are unconfirmed and it is unclear what aspects of synaptic plasticity, if at all, mediate increases in motor performance. Taken together, while clinical studies unequivocally showed that SES can increase motor performance, the mechanisms through which SES operates are unclear. A better understanding of these mechanisms may aid in optimizing rehabilitative SES protocols for neurological patients suffering from motor dysfunctions.

1.3 THESIS AIMS AND OUTLINE

The present thesis primarily aims to examine the effects of SES on the acquisition, consolidation, and interlimb transfer of a manual visuomotor skill in healthy young adults. As a secondary aim, potential mechanisms underlying SES-induced effects on motor performance are evaluated with TMS and EEG. To address these questions, chapter 2 provides a detailed narrative review of the available literature and presents hypotheses that are examined in chapters 3-5 of this thesis. Specifically, we evaluated whether SES alone and in combination with motor practice increases motor performance in a healthy young
population, and whether such effects are specific to the stimulated hand or transferable to the non-stimulated contralateral hand (chapter 3). In addition, we examined not only the immediate, but also the delayed effects of SES after 24 hours and seven days on motor performance (chapter 4). In chapters 3 and 4, we used TMS to examine cortical plasticity by quantifying corticospinal, intracortical, and interhemispheric excitability within and between M1s. Because TMS is only able to measure one structure and complex motor skill acquisition, consolidation, and transfer involve multiple brain structures, we assessed the relative importance of activity within brain areas and connectivity between brain areas for the SES-induced immediate and delayed effects on the acquisition, consolidation, and transfer of motor skills using EEG (chapter 5). A general discussion of the information obtained in chapters 2-5 will be provided in chapter 6, culminating in the conclusion of the present thesis.
REFERENCES


