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Interactions between learning and LTP/D-like plasticity in human motor cortex studied with TMS

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Introduction: Learning may alter rapidly the output organization of adult motor cortex. Long-term potentiation (LTP) and long-term depression (LTD) form important mechanisms for learning-induced cortical plasticity. Evidence in favour of this hypothesis was provided in rat primary motor cortex (M1) by showing that motor learning reduced the subsequent induction of LTP but increased LTD (Rioullet-Pedotti et al. 2000). Whether a similar relationship exists in humans is unknown.

Methods: We induced LTP-like and LTD-like plasticity in the M1 of 12 healthy subjects by paired associative stimulation (PAS) (Stefan et al. 2000). PAS consisted of 200 pairs of electrical stimulation of the right median nerve followed by focal TMS of the hand area of the left M1 at an interval equalling the individual N20 latency of the median nerve somatosensory evoked cortical potential (PASN20) or N20 - 5 ms (PASN20-5).

Results: PASN20 induced reliably an LTP-like long-lasting (> 30 min) increase in motor evoked potentials from the left M1 to a thumb abductor muscle of the right hand, whereas PASN20-5 induced a LTD-like decrease. Repeated fastest possible thumb abduction movements resulted in learning, defined by an increase in maximum peak acceleration of the practiced movements. Learning prevented the subsequent induction of LTP-like plasticity by PASN20, but enhanced the induction of LTD-like plasticity by PASN20-5. Further experiments showed that LTD-like plasticity enhanced subsequent motor learning. **Conclusions:** Findings strongly support the contention that learning in human M1 occurs through LTP-like mechanisms. The interactions between learning and LTP/D-like plasticity are best explained by the Bienenstock-Munroe-Cooper theory (Bienenstock et al. 1982) of bi-directional synaptic plasticity.

Bienenstock EL et al. 1982, *J Neurosci* 2: 32

Rioullet-Pedotti M et al. 2000, *Science* 290: 533

Stefan K et al. 2000, *Brain* 123: 572

Where applicable, the experiments described here conform with Physiological Society ethical requirements.

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Plasticity in the leg representation of the motor cortex and in the spinal cord in human subjects

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Motor skill acquisition is associated with changes in the cortical representation of specific muscles involved in the task (Pascual-Leone et al. 1994; Karni et al. 1995; Classen et al. 1998; Lotze et al. 2003; Perez et al., 2004). It is less well understood whether plastic changes associated to motor skill acquisition also take place in the spinal cord. Here we report a series of experiments

in which we investigated the effect of motor skill training on leg motor cortical and spinal neuronal circuits.

In healthy volunteers we tested the effect of 32 min training of two motor tasks with different degree of difficulty, a novel motor skill task involving the ankle muscles and a control task involving simple voluntary dorsi- and plantarflexion movements. We assessed tibialis anterior motor evoked potentials (MEPs) and soleus H-reflex size before and after training. We observed an increase of the MEP size and a decrease in the soleus H-reflex size following the motor skill training session. No changes were observed after the control task. To elucidate the mechanisms underlying the increased MEPs size we tested intracortical inhibition and facilitation using the paired-pulse TMS technique. Our results showed a decrease in intracortical inhibition with no changes in intracortical facilitation following the motor skill training, suggesting that removal of cortical inhibition may contribute to training-induced cortical plasticity. To explore the mechanisms contributing to the H-reflex depression we measured the size of the long-latency depression of the soleus H-reflex evoked by peroneal nerve stimulation (D1 inhibition) and the size of the monosynaptic Ia facilitation of the soleus H-reflex evoked by femoral nerve stimulation. The D1 inhibition was increased and the femoral nerve facilitation was decreased following the motor skill training, suggesting an increase in presynaptic inhibition of Ia afferents. Together these observations suggest that selective changes in cortical as well as spinal neuronal mechanisms occur during acquisition of a novel motor skill involving the ankle muscles in healthy humans.

The increased leg motor cortical excitability observed in our study in relation to motor skill acquisition likely reflects adaptations in the motor cortex related to the difficulty in the motor task. The increased presynaptic gating of sensory inputs to spinal motoneurons during motor skill acquisition may ensure that the motor cortex could control the movement based on integration of visual and proprioceptive input relatively undisturbed by the influence of the sensory feedback at the spinal level. In other words these finding could reflect a shift of importance in the control of the movement from spinal feedback mechanisms to direct cortical control. Classen et al. (1998). *J Neurophysiol* 79, 1117-1123.

Karni et al. (1995). *Nature* 377, 155-158.

Lotze et al. (2003). *Brain* 126, 866-872.

Pascual-Leone et al. (1994). *Science* 263, 1287-1289.

Perez et al. (2004). *Exp Brain Res* 159, 197-205.

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Exploring the metaplasticity of human motor cortex

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Recent experimental work in animals has emphasized the importance of homeostatic plasticity as a means of stabilising the properties of neuronal circuits. We have established a paradigm that

can be used to probe homeostatic-like plasticity at a regional level in the intact human cortex (1,2). The paradigm combines two transcranial stimulation techniques that can produce long-term effects on the excitability of corticospinal output neurones: transcranial direct current stimulation (TDCS) and repetitive transcranial magnetic stimulation (rTMS) of the left primary motor hand area.

In healthy individuals, facilitatory pre-conditioning with anodal TDCS caused a subsequent period of rTMS to reduce corticospinal excitability, whereas inhibitory pre-conditioning with cathodal TDCS tuned the conditioning effect of rTMS towards facilitation. Hence, the magnitude and direction of after-effects induced by slow or fast rTMS depended on the state of cortical excitability before stimulation and was tuned by pre-conditioning with TDCS. This implies that changing the initial state of the motor cortex by a period of DC polarisation can reverse the conditioning effects of rTMS.

These findings indicate a homeostatic mechanism in human motor cortex that stabilizes corticospinal excitability within a physiologically useful range. This type of metaplasticity is of relevance to the therapeutic application of transcranial cortex stimulation in neuropsychiatric disorders.

Siebnner HR, Lang N, Rizzo V, Nitsche MA, Paulus W, Lemon RN, Rothwell JC (2004) Preconditioning of low-frequency repetitive transcranial magnetic stimulation with transcranial direct current stimulation: evidence for homeostatic plasticity in the human motor cortex. *J Neurosci* 24(13):3379-3385

Lang N, Siebnner H, Ernst D, Nitsche MA, Paulus W, Lemon RN, Rothwell J (2004) Pre-conditioning with transcranial DC stimulation sensitizes the motor cortex to rapid-rate TMS and controls the direction of after-effects. *Biol Psychiatry* 56(9):634-639

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