Journal Club

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Spike-Timing Dependent Plasticity in Humans

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Review of Thabit et al.

Activity-driven modulation of synaptic strength plays a crucial role in shaping neural circuits in both physiological and pathological conditions. Long-term potentiation (LTP) and long-term depression (LTD) were first discovered *in vitro* as the persistent strengthening and weakening of synaptic efficacy in response to brief but patterned stimuli (Bliss and Lomo, 1973). With the experimental accessibility of brain slices, much of our knowledge on LTP and LTD has come from *in vitro* studies. Thus, much current effort is focused on validating these *in vitro* findings *in vivo*, such as in freely behaving animals. Interestingly, some studies have already taken this validation one step further, to humans.

LTP/LTD can be induced in brain slices either by presynaptic stimulation with trains of electrical pulses, such as theta burst stimulation, or by pairing presynaptic and postsynaptic stimuli separated by millisecond time intervals, such as spike-timing-dependent plasticity (STDP)-inducing protocols (Bi and Poo, 2001). These stimulation protocols have inspired the design of novel strategies for the use of transcranial magnetic stimulation (TMS) in the study of human physiology and neurorehabilitation. In general, high-frequency ($\geq$1 Hz) repetitive TMS increases, whereas low-frequency ($<$1 Hz) TMS decreases, cortical excitability as assessed by the amplitude of motor-evoked potentials (MEPs) (for review, see Sandrini et al., 2010). However, repetitive TMS, particularly at higher frequencies, carries an increased risk of inducing seizures (for review, see Ridding and Rothwell, 2007). Subsequently, Stefan et al. (2000) developed a pairing protocol in which low-frequency median nerve stimulation is coupled with a single pulse of TMS stimulation in contralateral primary motor (M1) cortex. Similar to the findings in STDP, this protocol increases or decreases motor cortex excitability when TMS precedes or follows peripheral nerve stimulation, respectively. Because this protocol associates electrical stimuli with TMS, it is unclear whether the combination of endogenous M1 activity with TMS, a much-preferred paradigm in neurorehabilitation, is sufficient to induce motor cortical plasticity.

In a recent issue of *The Journal of Neuroscience*, Thabit et al. (2010) described a modified pairing protocol in which TMS was paired with a natural movement-related activity in M1, which resulted from voluntary thumb abduction at different interstimulus intervals. The amplitudes of MEPs of behaviorally trained and untrained muscles were measured as the functional readouts of corticospinal excitability.

This pairing protocol modulated the amplitudes of MEPs in the abductor pollicis brevis muscles (responsible of thumb abduction), but not the abductor digiti minimi muscles (not involved in the task). When TMS was given 50 ms before motor training, a significant increase in the amplitude of MEPs was detectable almost immediately and lasted for 15 min. This sequential stimulation also shortened the reaction time in the simple reaction task without affecting the resting motor threshold. Together, these data suggested that M1 cortical plasticity might have been enhanced. Furthermore, there were no significant changes either in the pinch force of both hands or in the excitability of spinal motor neurons, as determined by F-wave amplitude. Thus, Thabit et al. (2010) concluded that the primary locus of TMS/movement-induced plasticity is in the motor cortex of the brain, rather than in the spinal cord motor circuits.

This finding is intriguing because the signals evoked by a voluntary movement such as thumb abduction are relayed primarily via corticospinal tracts that originate in M1 and modulate intrinsic motor circuits in the spinal cord. In addition, the extent to which TMS pulses activate subcortical areas important in voluntary motor control is unclear. Therefore, the pairing effect of voluntary movement with TMS could, in theory, affect subcortical regions and spinal levels as well as M1 (Petersen et al., 2010). Further studies will be needed to test whether this is true, and if so, how important plasticity in each area is under different stimulus protocols and conditions.

Another important point to consider is whether the duration of the cortical plasticity induced by TMS–movement pairing is effective enough for use in clinical ther-

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apy. Thabit et al. (2010) state that their pairing protocol was able to induce LTP/LTD-like plasticity immediately after training. However, the longest duration of the motor improvement reported was only 15 min. Because this strategy carries therapeutic potential for neurorehabilitation in the future, it is important to determine whether permanent effects could be achieved by a more intensive training program.

The authors next investigated the role of inhibitory circuits in the expression of cortical plasticity induced in this paradigm by measuring the short interval cortical inhibition (SICI) and the silent period (SP). SICI refers to the inhibition of suprathreshold TMS-evoked responses after pre-exposure to subthreshold TMS stimuli in a short interstimulus interval. In contrast, SP refers to a TMS-induced cessation of electromyography activity of the targeted muscle. Pharmacological studies have shown that SICI can be increased by enhancing $GABA_A$ receptor-mediated transmission, whereas SP is prolonged by enhancing $GABA_B$ receptor-mediated activity (Chen, 2004; Ziemann, 2004). Here, no significant changes in the SICI were observed after training; however, the SP duration was significantly increased after treatment. The authors speculated that TMS/movement-induced plasticity might strengthen the $GABA_B$ receptor-mediated inhibition in addition to increasing the amplitude of MEPs.

It is, however, unclear how stronger neuronal inhibition due to increased $GABA_B$ receptor activity could contribute to increased synaptic efficacy in M1 cortex. In fact, reducing intracortical inhibition has previously been shown to contribute to increased motor excitability in response to repetitive TMS (Peinemann et al., 2000). Moreover, Stefan et al. (2002) observed only transient decrease in intracortical inhibition when pairing TMS and peripheral nerve stimulation. Further studies using pharmacological interventions and detailed kinetic analysis will be needed to explain these discrepancies.

The TMS–movement pairing protocol used by Thabit et al. (2010) resembles that used for the induction of STDP in *in vitro* studies. It has previously been shown that STDP causes bidirectional plasticity depending on the temporal order of presynaptic and postsynaptic stimuli in brain slices; if presynaptic stimulation occurs before or after postsynaptic depolarization, LTP or LTD is induced, respectively (Bi and Poo, 2001). Hence, Thabit et al. (2010) next sought to determine the effects of manipulating the sequence and intervals between TMS and movement onset. They found that the amplitude of MEPs was enhanced if TMS preceded movement-induced cortical signals by 50 ms. In contrast, MEP amplitude was depressed if TMS followed movement-induced signals by 100 ms. Thus, the protocol also produces bidirectional modulation of M1 motor cortical plasticity. This is an interesting finding that could translate many basic neuroscience findings into clinical interventions.

The authors may have oversimplified the similarity between the TMS/movement-induced plasticity in humans and STDP in laboratory animals, however. Although both cases use the relative timing of two stimuli to induce bidirectional plasticity, the underlying mechanisms might be different. In most LTP/LTD studies in slice preparations, the induction protocols involve selective focal stimulations onto specific fibers in targeted areas; changes in the EPSPs are measured as readouts. In contrast, TMS has relatively low spatial resolution. TMS stimulates a mixture of different types of neurons, some of which innervate locally and could be inhibitory, whereas others send long-distance projections out of the stimulation area and could cause widespread effects in different brain systems. In addition, TMS affects glial cells and blood vessels, producing unknown effects on plasticity and behavior. Thus, it is likely that TMS/movement-induced plasticity is an interaction of this pairing protocol with a host of unexplored homeostatic regulations ongoing in the brain.

In summary, the article by Thabit et al. (2010) has demonstrated a new and noninvasive method for inducing M1 cortical plasticity in humans. Based on the protocol for the induction of STDP in animal models, the authors combined the use of TMS with voluntary movement to manipulate M1 cortical plasticity in humans. This new strategy offers the promise of future applications in neurorehabilitation, once its neurophysiological basis is better understood.

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