

● PERSPECTIVE

Enhanced motor cortex excitability after spinal cord injury

Transcranial magnetic stimulation (TMS) represents a useful non-invasive approach to studying cortical physiology, in addition to the descending motor pathways (Hallett, 2000), and may also be used to investigate the intracortical facilitatory and inhibitory mechanisms. TMS studies evaluating motor cortex excitability after incomplete spinal cord injury (SCI) have shown that the activity of intracortical inhibitory circuits may be reduced in these patients. We briefly illustrate and discuss here the most important TMS studies investigating cortical excitability in subjects with SCI.

Cortical inhibition has been initially studied by investigating motor evoked potential (MEP) and suppression of voluntary contraction (SVC) in response to TMS applied over the motor cortex (Davey et al., 1998). Both latency and threshold for SVC were increased in the patients with SCI. However, the SVC was found to occur at longer latency than the MEPs. While the latency difference between SVC and MEP response was ~13.4 ms in control subjects, the patients with SCI showed a difference of ~25.3 ms. This finding suggests that a longer pathway is involved in producing the suppression, presumably involving interneurons within the motor cortex. Some of these changes are likely to be in part the result of alterations to the corticospinal system (the destruction of corticospinal axons or slowing of conduction velocity at the level of the lesion in the spinal cord). However, the changes in cortical inhibition (reflected by SVC) are, at least in part, likely to be the result of altered function within the brain.

Intracortical inhibition is more usually studied by applying a subthreshold conditioning stimulus before the suprathreshold test stimulus at short interstimulus intervals. The resulting inhibition of the MEP is called short-interval intracortical inhibition (SICI) (Rossini et al., 2015).

Two single-subject reports have shown that SICI is reduced after incomplete SCI (Shimizu et al., 2000; Saturno et al., 2008). However, SICI was examined only with one single conditioning and test stimulus intensity. Studying SICI over a range of intensities has become increasingly important for the recruitment of neurons by the test stimulus pulse that are differentially susceptible to SICI modulation, and the contribution from short-interval intracortical facilitation activated by the conditioning stimulus cannot be excluded. It should also be considered that the stimulus intensities chosen to assess SICI are frequently based on the motor threshold, thus damage to descending motor fibers in SCI will invariably raise these TMS intensities resulting in overactivation of the intact

motor cortex. Roy et al. (2015) also found a reduced SICI in patients with chronic SCI; however, when the absolute stimulation intensities were matched between patients and healthy controls in terms of maximum stimulator output, both U-shaped SICI recruitment curves were produced by similar conditioning stimulation intensities.

Motor cortical excitability can also be estimated utilizing the amplitude and recruitment curve of MEP following TMS (Rossini et al., 2015). With increasing stimulus intensity, the amplitude of the MEP increases until it reaches a plateau level in healthy subjects. This increase in MEP amplitude is referred to as MEP recruitment curve. In a recent study (Nardone et al., 2015a), MEP amplitude and recruitment curve were evaluated in five subjects with good recovery after traumatic incomplete cervical SCI. While RMT did not differ significantly between patients and control subjects, the slope of MEP recruitment curve was significantly increased in the patients. This abnormal finding was supposed to represent an adaptive response after SCI. The impaired ability of the motor cortex to generate proper voluntary movement may be compensated by increasing spinal excitability.

The easily performed measurement of MEP recruitment curve may thus provide a useful additional tool to improve the assessment and monitoring of motor cortical function in subjects with SCI.

To further clarify the mechanisms of cortical reorganization after SCI, also a non-invasive paired TMS protocol for the investigation of the corticospinal I-waves, the so-called I-wave facilitation, has been used in eight patients with cervical SCI (Nardone et al., 2015b).

A significantly different pattern of I-wave facilitation was found between SCI patients with normal and abnormal central motor conduction (CMCT), and healthy controls. The group with normal CMCT showed increased I-wave facilitation, while the group with abnormal CMCT showed lower I-wave facilitation compared to a control group. The facilitatory I-wave interaction occurs at the level of the motor cortex, and the mechanisms responsible for the production of I-waves are under control of GABA-related inhibition. Therefore, the findings of this small sample preliminary study provide further physiological evidence of increased motor cortical excitability in patients with preserved corticospinal projections, which is possibly due to decreased GABAergic intracortical inhibition. Again, the excitability of networks producing short-interval intracortical facilitation could also increase in SCI subjects as a mechanism to enhance activation of residual corticospinal tract pathways and thus compensate for the impaired motor cortex ability to generate appropriate voluntary movements.

Another paradigm used to assess inhibitory processes is the duration of the cortical silent period (CSP) evoked by TMS, which is measured from the MEP onset to the

return of electromyography activity. Studies using the CSP in SCI patients yielded contradictory results (Shimizu et al., 2000; Lotze et al., 2006; Freund et al., 2011).

Recently, the CSP was evaluated during a fatiguing muscle exercise in 5 patients with incomplete cervical SCI and in 5 healthy subjects (Nardone et al., 2013). The physiological lengthening of CSP end latency during fatigue was not observed in the SCI patients. This reduced intracortical inhibition is also probably secondary to decreased activity of the GABAergic inhibitory interneurons that modulate the corticomotoneuronal output, and could also represent a 'positive' neuroplastic response in an attempt to compensate for the loss of corticospinal axons. The investigation of motor cortex excitability during fatiguing exercise may therefore shed light on the role of exercise therapy in promoting brain reorganization and functional recovery in humans.

The above-mentioned studies seem to point to an increased motor cortex excitability after SCI. Nevertheless, it should be noted that most studies have been performed in patients with incomplete SCI and/or good motor recovery.

So far there is no sufficient experimental evidence to determine whether this abnormal intracortical inhibition after SCI represents an adaptive or maladaptive response. It can be speculated that after SCI the primary motor cortex attempts to compensate for its inability to generate proper voluntary movement by increasing resting motor cortical excitability.

In conclusion, several TMS techniques, including the measurement of SICI, MEP RC, or I-wave facilitation, may provide a useful additional tool to improve the assessment and monitoring of motor cortical function in subjects with SCI, and could therefore be used in clinical neurorehabilitation.

Increasing our knowledge of the corticospinal excitability changes in the functional recovery after SCI may also support the development of effective therapeutic strategies. The finding of abnormally reduced inhibition in the motor cortex after chronic SCI, which has been highlighted in the present paper, may contribute to the understanding of the effects of interventions that can modulate cortical excitability. In fact, appropriately testing cortical physiology is of crucial importance before treating SCI patients with neuromodulatory techniques, in particular repetitive TMS and transcranial direct current stimulation.

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