LETTER TO THE EDITOR

Understanding cortical topographical changes in liminally contractable muscles in SCI: importance of all mechanisms of neural dysfunction

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We seek to discuss recent findings published in *Spinal Cord* by Cortes *et al.*¹ We believe it is important to consider why Cortes', as well as previous findings in the field of spinal cord injury (SCI), may explain muscle paralysis and how they can be used to drive rehabilitative therapies for paretic muscles for individuals with complete SCI (cSCI) to ultimately improve functional independence.

Recent research efforts have aimed to determine why rehabilitative outcomes remain limited following SCI. One hypothesis generated based on rodent and primate work argues that spared neural structures reorganize in a way so as to represent spared strong muscles innervated rostral to the injury instead of weak muscles innervated below the level of injury.^{2,3} In their recent study published in *Spinal Cord* by Cortes *et al.*,¹ the authors aimed to determine whether a similar pattern of reorganization was present in humans with SCI. The authors employed a noninvasive, neurophysiological technique called transcranial magnetic stimulation (TMS) to evaluate cortical representations of muscles that were extremely weakened after SCI. Overall, Cortes *et al.*¹ found that potentials could be evoked at rest in muscles with low muscle power (MP) (MP = 1) for all subjects with SCI.^{2,4} The observed evoked potential properties in subjects with SCI, including evoked thresholds, amplitudes and latencies, did not significantly differ from healthy controls. Cortes *et al.*¹ were also able to collect and analyze TMS motor maps in all participants with SCI and healthy participants. Compared to the control range, the authors found that only 3 out of 10 subjects demonstrated a substantially reduced motor map size in comparison to healthy controls. On the basis of this result, the authors suggested that in the chronic phase of injury, muscles with liminal voluntary activation have similar topographical representations in the motor cortex to healthy controls. In addition, the authors argue that because topographical representations of weaker muscles are intact, rehabilitation programs that work to improve motor control may help facilitate functional recovery.⁵

We believe that Cortes' study is timely and highlights several topics that need to be considered in the field of neurorehabilitation in SCI. First, after SCI, it has been shown that the majority of individuals with SCI have significantly altered motor evoked potential (MEP) properties that likely limit functional recovery.^{4,6–8} What is intriguing, though, is that Cortes found that the evoked potential properties, including motor threshold, amplitude and latency, did not differ between the participants with SCI and healthy controls. At initial examination, the result from Cortes differs from previous results from other studies. However, we believe that the difference in Cortes' findings can be explained based on previous work in the field of SCI.

Of note, we propose that based on a vast body of literature, thresholds to evoke a muscle response in muscles weakened after SCI

can be similar to healthy controls. The factors that appear to influence evoked potential thresholds are: (1) the level of SCI injury, (2) muscle evaluated by TMS and (3) structural damage to motor pathways. For example, Cariga *et al.*⁹ observed that the motor threshold for MEPs was lower for paravertebral muscles rostral to the injury, unchanged for muscles innervated within the injury and increased in muscles innervated more than four levels below the lesion; a finding that has since been replicated.^{7,10,11} This suggests that the level of innervation of the muscle chosen for evaluation with TMS in relation to the level of injury may affect thresholds. Such previous work corroborates Cortes' findings. Specifically, in Cortes' subject pool, TMS was always performed on a muscle innervated at or within two cervical levels of the lesion. This suggests that Cortes' observation that subjects with SCI have a similar threshold to controls may not be contradictory, but rather the influence of the muscles evaluated. Thus, we recommend that future studies will need to account for patient heterogeneity since baseline corticospinal excitability can be influenced by intrinsic subject factors.

Next, one of the most interesting findings from Cortes *et al.*¹ is that cortical representations of weakened muscles did not differ from healthy controls. This finding is in contrast to what has long been believed to occur following SCI. The authors hypothesized that the difference in results may be related to the neural circuitry activated by TMS. However, we would like to draw attention to some methodological issues that may have contributed to their observed findings. Traditionally, cortical mapping studies define a map site as active if MEPs are between 30 and 50 μ V at rest.¹² However, Cortes' defined a motor map site as active if the MEP that was elicited was at least 1/8 of the maximum observed MEP. Use of such a moving baseline may have contributed to substantial variability of maps, given that MEP amplitudes greatly varied across controls and subjects. For example, one control subject had a max amplitude of 1.7 mV. This suggests that for this subject, only sites that demonstrated MEPs >212 μ V were used to calculate area. Thus, this subject's map may have been underestimated, since sites that still elicited MEPs around 50 μ V were not included. In contrast, for their subject with SCI having a max MEP amplitude of 121 μ V, a site only needed to display MEPs >15 μ V to be considered within the map area. Thus, map sizes for the control group were likely underestimated, while the motor map sizes for the group with SCI were overestimated.

Although cortical representations of weakened muscles did not differ from healthy controls, a careful analysis of Cortes' subject pool suggests that future studies should consider how the severity of injury influences weakened muscle map size. Cortes' results demonstrated that the few individuals that had reduced maps in comparison to

controls were classified as American Spinal Injury Association Impairment Scale (AIS) A (complete injury; $n=2$) or AIS B (sensory incomplete; $n=3$), while those with unchanged maps were mainly AIS C ($n=3$). This result is not surprising, given that *in vivo* observations have already demonstrated that rats suffering from a complete motor SCI display no cortical representations to muscles that were de-efferented at 5 months post injury.³ However, given this finding, we therefore think it is important for future studies to include only those with motor complete (AIS A or B) or motor incomplete (AIS C or D), such that a more accurate group analysis can be completed on the population.

Cortes' work highlights a key question in the field of SCI neurorehabilitation: if the evoked potential properties and motor cortical maps in subjects with no MP are similar to those in healthy subjects, then what explains the substantial loss of volitional motor function in subjects with MP=1? We believe, the answer to this question may be addressable when multiple networks involved in volitional movement are considered, as shown in Figure 1.

TMS is a valuable tool to understand the corticospinal connections between the motor cortex and innervated muscles. However, motor function is based on volitional recruitment of these connections. Thus, even if TMS outcomes demonstrated 'normal' corticospinal outputs (based on authors' interpretation), poor volitional recruitment of connections between the motor cortex and innervated muscles could explain muscle paralysis. For example, higher motor networks required for motor recovery following SCI have been found to show

reduced activation or poor regulation (Figure 1, mechanism 1).^{8,13,14} In a similar notion, hyperexcitability of muscles innervated rostral to the injury could also contribute to muscle paralysis.^{11,15} Thus, if the stronger and weaker muscle shared substantial topographical overlap and the strong muscle was more readily excitable, activation of the weak muscle could become overshadowed during volitional movement. Second, dysfunction in pathways not directly assessed by TMS, including extrapyramidal pathways originating from the red nucleus or brain stem, could exaggerate muscle paralysis¹⁶ (Figure 1, mechanism 2). This is because both volitional upper limb function and recovery after SCI has been linked to activity, sprouting and re-routing of reticulospinal or propriospinal pathways.¹⁷ Third, loss of sensory-proprioceptive input may also contribute to paralysis or lack of volitional motor function, given that a lack of knowledge regarding joints and muscles in space can affect their activation/use in volitional activities^{18,19} (Figure 1, mechanism 3). Finally, the importance of the pathways within the spinal cord on MP can also not be overlooked²⁰ (Figure 1, mechanism 4). Bunday and Perez⁸ have suggested that spinal motoneurons likely drive corticospinal excitability after SCI. This suggests that even in the presence of patent cortical circuitry, changes in spinal cord and/or peripheral circuitry could influence MP.

In the end, one important question remains: what techniques can be used to improve MP in weakened muscles after SCI with 'normal' physiological properties? The solution to this problem, we believe, will likely be driven by the neural circuitry that is altered after SCI (Figure 1). For example, only targeting one location of neural dysfunction, such as somatosensory stimulation to alter sensory input, may be effective in subjects with presumably intact motor/sensory pathways and a residual motor function greater than medical research council (MRC) grade 3.^{19,21} In contrast, we believe for subjects with extreme paralysis after SCI, such as those enrolled in Cortes' study, several adjunctive approaches will need to be utilized to address the multiple loci of nervous system dysfunction (Figure 1). A recent study by Donati *et al.*²² supports this position. Donati found that training combining virtual reality (motor imagery), tactile stimulation (proprioceptive feedback) and robotic actuators could significantly improve neurological recovery in chronic SCI paraplegics—wherein, 50% of subjects were upgraded from a complete to incomplete injury.²² Thus, moving forward close together, we believe it is important for future studies to consider all possible mechanisms of neural dysfunction before designing rehabilitation paradigms to improve MP in weakened muscles.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Figure 1 Four areas of neural dysfunction beyond those assessed with TMS (shown with thick red area) that could contribute to loss of motor function. Red arrows denote motor pathways and purple arrows denote sensory pathways. (1) Higher order cortices; (2) brain stem and red nucleus mediated pathways; (3) sensory deficiencies; and (4) spinal cord plasticity/inhibition. A full color version of this figure is available at the *Spinal Cord* journal online.

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