Authors' response

We thank Professor Janet Taylor and Ms. Siobhan Fitzpatrick for their comments pertinent to our study. We do agree with their comment that the intensity levels of peripheral nerve stimuli (PNS) applied in our experiments may not have been sufficiently high. However, when we selected the PNS intensities, we had to take into consideration participants' comfort. Specifically, in a pilot study (before the one described in the article) we discovered that many participants were not able to tolerate high stimulation intensities. Therefore, for the purpose of this study we adjusted the stimulation levels to the levels our participants were able to tolerate. Hence, the stimulation levels presented in our article also reflect what individuals were willing and able to tolerate during the intervention.

We also agree that the timing between pre- and postsynaptic activations was not ideal. We did acknowledge criticality of the spike-timing-dependency of the system and we discussed this in the Introduction, but we did not discuss this point fully in the later sections of the manuscript, which may have provoked Professor Taylor and Ms. Fitzpatrick's criticism. However, we would also like to note that we actually tested other timings as well, and we were not able to clearly distinguish which of them was more advantageous. Although this may have resulted from the above-mentioned lower stimulation intensity, we are of the opinion that the high variability in the outcomes of the paired associative stimulation (PAS), which we pointed out in our article, may be a key issue with PAS. If this is the case, and if the effects of PAS are highly variable, this may be a major obstacle in applying this method as a therapeutic intervention in a clinical setting.

It was our original intent to start using this technique as a therapeutic intervention for people with spinal cord injury (SCI). This particular study was meant to be our first step towards use of this therapeutic intervention in the SCI population, and we intended to use this particular study to determine the best stimulation parameters for clinical use. Although we noticed the spike-timing-dependency of this phenomenon, as aforementioned, we thought that this phenomenon should be more robust (not very dependent on small errors in timing) for it to have practical value in a clinical setting. In a clinical setting, it is not practical to have a person delivering the therapy to set the spike-timing perfectly every single time and for every single individual. Also, the observed variations of MEP and F-wave latencies were up to several milliseconds and varied considerably among participants. Thus, if this method is to be used in a clinical setting it has to be somewhat robust despite minor variations in timing.

While we appreciate Professor Taylor and Ms. Fitzpatrick's comments, and we agree with many of them, we still believe that our study raised a few questions that should be considered by the community before this technique is applied in a clinical setting. We sincerely hope that a solution to this problem can be found, as our patients need new and innovative methods to help them regain function, and we as a team believe that this particular method, namely PAS, may be a good candidate to help us achieve this goal.

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