In the Journal Club article, "Improving the potential of neuroplasticity", Ruge and colleagues discuss concerns related to portions of the methodology used in our recent study (Buch et al., 2011), in which repeated paired-pulse transcranial magnetic stimulation (TMS) is used to selectively modulate physiological connectivity between the ventral premotor cortex (PMv) and primary motor cortex (M1) in humans. The Journal Club article summarizes the key findings of our study quite nicely. However, we would like to take the opportunity to respond to the specific criticisms that were levied, because several of these points have either been resolved previously in the literature, or are directly addressed by one of the experiments we conducted.

Ruge and colleagues' initial criticism is focused on the proximity of the PMv and M1 stimulation sites. In order to prevent any misunderstanding, we emphasize that in our study the inter-coil distance ranged 5.5–7 cm apart on the scalp. Ruge and colleagues imply that this proximity comes at the expense of optimal coil orientation for stimulation of PMv and results in a coil configuration that could promote passive current spread from PMv stimulation into M1. We do agree that current hardware constraints limiting the physical dimensions, induced field strength, and heating rate of TMS coils are a major impediment to exploring many multi-region functional interactions in the brain with this technique. However, we feel that there is sufficient evidence to discount these concerns for the PMv–M1 pathway. First, the same coil configuration has been used for these sites in several TMS studies in different laboratories, with PMv–M1 TMS effects displaying both anatomical and functional specificity (Davare et al., 2006; Davare et al., 2008; Baumer et al., 2009; Davare et al., 2009; Davare et al., 2010; Houdayer et al., 2012). Moreover, two of the studies showed that paired-pulse stimulation applied to M1 with identical parameters, which is specifically designed to control for current spread, produces quite distinct effects both while at rest and during behavioral tasks (Buch et al., 2010; Davare et al., 2009). Finally, if the effects observed after plasticity induction resulted from passive current spread, then one would expect that reversed-order conditioning, in which M1 was repeatedly stimulated before PMv, would have led to a similar effect, because it would have also resulted in M1 being stimulated twice. We found however, that reversed-order stimulation did not lead to the same plasticity effect, but instead resulted in the opposite pattern of plasticity-related changes.

Ruge and colleagues also suggest that the coil orientation and stimulation intensity chosen for the pre-supplementary motor area (pre-SMA) site used in several of the control experiments may not have been adequate. In previous studies using either repetitive TMS or paired-pulse TMS stimulation, intensities of 90% resting-motor threshold (RMT) showed modulatory effects of pre-SMA on motor network connectivity (Neubert et al., 2010; Cattaneo et al., 2011). The coil configuration used here has been previously used effectively to stimulate the pre-SMA–M1 pathway, as well (Mars et al., 2009). We feel that these studies, which specifically target the pre-SMA, provide sufficient evidence that the 110% RMT intensity and coil orientation used in our experiments induced adequate stimulation of pre-SMA. Secondarily, there is some confusion in this section of the Journal Club article, because Ruge and colleagues sometimes refer to our control site as supplementary motor area (SMA) and sometimes to it being pre-SMA. We confirm for the reader that the control site was indeed pre-SMA and not SMA proper, and note that these are both functionally and anatomically distinct regions that can be reliably distinguished and identified in most people (Johansen-Berg et al., 2004). Also, it is possible to gain the impression from the Journal Club article that the pre-SMA location was not confirmed with magnetic resonance imaging. This was not the case however, and we remind the reader that all stimulation sites for all subjects are shown in Figure 1c.

The final point about which the authors expressed concern was the timing of the stimulation used in the experiments, implying that it is not known if the timings used in our experiment were appropriate. There are two potential issues to consider in relation to timing. First, it is important to know whether the

latency between the two TMS pulses applied to the two brain areas is sufficient for producing a significant effect on the resulting MEP, and this can only be discerned by studying multiple inter-stimulus intervals (ISIs). In fact, several previous studies using paired-pulse TMS to investigate both PMv–M1 and pre-SMA–M1 interactions have shown significant effects for the ISIs used here (Davare et al., 2009; Mars et al., 2009; Neubert et al., 2010). In fact, one of the main reasons for selecting the pre-SMA–M1 pathway as a control for the PMv–M1 pathway experiments is that both show paired-pulse effects for the same ISI. Second, when investigating these interactions within the context of a behavioral task, it is important to apply the TMS stimulation at a point that is time-locked to a particular behavioral event. Ruge and colleagues imply that the timing of the TMS with respect to this particular task may have been inappropriate. However, a previous study by our group explored this very issue with respect to this behavioral task, with the time-point used here showing a significant effect of PMv–M1 paired-pulse TMS (Buch et al., 2010).

In summary, we thank Ruge and colleagues for drawing the attention of readers to our paper and highlighting the novel contributions that it makes to the fields of neuroplasticity and neurorehabilitation. Although we disagree with some of the methodological criticisms levied here, we fully agree with the notion that novel non-invasive brain stimulation techniques targeting specific functional brain network interactions have the potential for rehabilitative application in a myriad of neurological and psychiatric disorders. Future improvements to non-invasive brain stimulation technology, as well as investigation combining these techniques with neuroimaging, will continue to move the field towards achieving this goal.

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