Sir,

Patients with congenital mirror movements have structural abnormalities of the corticospinal and transcallosal pathways, and functional deficits of interhemispheric inhibition and motor planning processes, which lead to the inability to perform independent hand movements (Gallea et al., 2013). In their Letter to the Editor, Brandaão et al. (2014) suggest that (i) the abnormal pyramidal decussation could be a biomarker to diagnose congenital mirror movements; and (ii) neuromodulation by way of artificial stimulation could be used as therapeutic means to influence interhemispheric inhibition and/or motor planning processes.

Congenital mirror movements is a developmental movement disorder and syndromic diagnosis is easily made, based on clinical examination (Bonnet et al., 2010), making the neuroimaging or neurophysiological evidence of abnormal pyramidal decussation rather obsolete for this purpose. Linking abnormal pyramidal decussation to a genetic cause of isolated congenital mirror movement has not been properly investigated to date. Comparison of the pyramidal tract morphology between patients with DCC mutation/deletion, RAD51 mutation/deletion and no mutation/deletion in DCC or RAD51 has not been investigated. Using transcranial magnetic stimulation (TMS) in a DCC-MM patient, it was demonstrated that each M1 cortex was abnormally connected to both sides of the spinal cord via separate crossed and uncrossed fast conducting corticospinal projections (Cincotta et al., 2003; Depienne et al., 2011). It is thus likely that abnormal pyramidal decussation is a common feature in both DCC-MM patients and RAD51-MM patients and that studying the pyramidal decussation would not help in guiding the genetic diagnosis.

The two neuromodulation techniques proposed by Brandão et al. (2014) have different principles of action: the repetitive TMS modulates the synaptic strength whereas transcranial direct current stimulation (tDCS) modulates the membrane polarity of the neurons (Wagner et al., 2007; Hoogendam et al., 2010). The repetitive TMS changes information transmission along specific pathways (Popa et al., 2013), whereas the tDCS affects local excitability under the stimulation site (Lang et al., 2004). For instance, repetitive TMS applied to one hemisphere impacts the interhemispheric inhibition exerted from the stimulated hemisphere to the other one (Gilio et al., 2003; Tsutsumi et al., 2013), whereas transcallosal inhibition is not affected using tDCS (Lang et al., 2004). In contrast, intrahemispheric connectivity between the supplementary motor area and M1 is impacted through both repetitive TMS (Matsunaga et al., 2005; Hamada et al., 2009; Arai et al., 2012) and tDCS (Hayduk-Costa et al., 2013; Vollmann et al., 2013). At the behavioural level, repetitive TMS applied to one hemisphere also modifies the reaction time of both contralateral and ipsilateral hand movements (Huang et al., 2005). Things are far less clear concerning tDCS: stimulation of the dominant hemisphere impacts on the performance of the ipsilateral hand, which is not the case after tDCS of the non-dominant hemisphere (Vines et al., 2008). The tDCS associated with motor training over consecutive days selectively enhances skill acquisition and consolidation compared to placebo stimulation (Reis et al., 2009).
Both repetitive TMS and tDCS have been used as means to reduce symptom severity in stroke and movement disorder patients (Popa et al., 2013; Marquez et al., 2013). The use of a neuromodulation as a therapeutic method must take into account the nature of the patients’ deficits. On the one hand, patients with congenital mirror movements in our study have structural abnormalities of the transcallosal pathways, which mediate interhemispheric inhibition. To our knowledge, there is no proof that tDCS can modulate the anatomical structure of brain pathways in humans, whereas high frequency repetitive TMS might modify the white matter structure in patients with structural deficits (Allendorfer et al., 2012; Peng et al., 2012). As this technique influences both brain structure and interhemispheric inhibition, repetitive TMS should be preferentially used to modify transcallosal communication and interhemispheric inhibition over multiple sessions, over several weeks (Fig. 1A). On the other hand, patients also had an abnormal functional drive from the supplementary motor area to M1 in the hemisphere contralateral to the mirror hand, without structural intrahemispheric abnormalities. Local changes of supplementary motor area excitability associated with motor training would refrain from transmitting the motor program to both hemispheres. The tDCS using small electrodes with more focal effects would allow this change, keeping with the normal course of physiological processes (Fig. 1B), whereas the repetitive TMS would force synaptic transmission and disrupt the chains of facilitation/inhibition processes involved in the control of hand movements. Therefore, it is theoretically possible to modulate functional connectivity in interhemispheric and intrahemispheric pathways.

Figure 1: Set-up suggestion using non-invasive brain stimulation for congenital mirror movement rehabilitation. (A) In congenital mirror movements, functional MRI results showed an abnormal bilateral drive from the supplementary motor area (SMA) to the M1 during unimanual movement (red arrows, upper panel; Gallea et al., 2013). Excitatory repetitive TMS (rTMS) can be applied either alone to one M1 or as paired-pulse rTMS of the target M1 and the ipsilateral supplementary motor area (middle panel). This should enhance the inhibitory drive from the stimulated M1 to the contralateral M1 (grey arrow). If a functional MRI connectivity study would be conducted after rTMS, it should show: normal unilateral SMA-M1 coupling (red arrow, lower panel), and decreased drive from SMA and M1 ipsilateral to the stimulation towards the contralateral M1 (blue arrows, lower panel) during attempted unimanual actions. (B) In this three-lead transcranial direct current stimulation (tDCS) set-up using mini-electrodes, the anode is placed over the target M1, while two cathodes are placed over the contralateral M1 and ipsilateral SMA. The tDCS would be applied during unimanual training (voluntary rhythmic movements of the contralateral hand while the ipsilateral hand is constrained). Ideally, such potentiated exercises should (i) raise the excitability of the target M1, (ii) reduce the excitability of contralateral M1, (iii) enhance the excitatory drive from the ipsilateral SMA to the target M1 (small red arrow), (iv) enhance the excitatory drive from the pyramidal neurons in contralateral M1 to the inhibitory interneurons in the target M1 (big red arrow), and (v) reduce the functional coupling between the ipsilateral SMA and contralateral M1 (blue arrow). Such boosted sessions of unimanual training should help to differentially modulate the excitability of each M1 when evaluated by single TMS pulses (lower panel). MEP = motor evoked potential.
intrahemispheric circuits using neuromodulation to circumvent structural corticospinal deficits. The behavioural results of neuromodulation, whether and how it potentially helps decreasing congenital mirror movements severity, will deepen our understanding of the link between structure and function underlying the lateralization of motor control.

References


