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Interhemispheric connectivity between distinct motor regions as a window into bimanual coordination

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Hinder MR. Interhemispheric connectivity between distinct motor regions as a window into bimanual coordination. *J Neurophysiol* 107: 1791–1794, 2012. First published November 30, 2011; doi:10.1152/jn.00822.2011.—Performing coordinated bimanual movement is a fundamental feature of the human motor system, with imaging techniques revealing the involvement of an extensive network of motor regions in both hemispheres. Using transcranial magnetic stimulation, Liuzzi et al. (*J Neurosci* 31: 9111–9117, 2011) recently extended our understanding of the neural correlates of motor actions by showing that the nature of the interhemispheric connectivity between primary and premotor regions may influence motor performance during a bimanual tapping task.

interhemispheric inhibition; transcranial magnetic stimulation; motor cortex; cortical connectivity; movements

THE ABILITY TO COORDINATE both (upper or lower) limbs simultaneously, or perform a task with one limb while maintaining quiescence in the contralateral limb, are fundamental characteristics of the human motor system and essential skills for successful execution of many everyday tasks. A large body of evidence, from imaging and single-cell recording studies, indicates that an extensive network of motor regions, including primary motor cortices, supplementary motor area, and premotor cortices are active during bimanual movements (e.g., Donchin et al. 1998; Tanji et al. 1988). Furthermore, interhemispheric communication between those active regions, via the fibers of the corpus callosum, is thought to be instrumental in permitting coordinated actions (e.g., Liuzzi et al. 2011; see also Meister et al. 2010).

Transcranial magnetic stimulation has proved to be a very useful tool in investigating this interhemispheric connectivity; the nature of the connectivity is determined by observing how the size of the evoked muscle response following a transcranial magnetic stimulation (TMS) stimulus applied to primary motor cortex (M1) is affected by a conditioning stimulus applied to the contralateral cortex a short time prior to the "test" stimuli (Ferbert et al. 1992). At rest, connectivity between the primary motor cortices is generally found to be inhibitory, and known as interhemispheric inhibition (IHI). During preparation and execution of a right-handed unimanual action, however, IHI from the passive (right, r) to active (left, l) cortex is reduced (disinhibited) to "release" the planned action, while IHI onto the nonresponding cortex is increased to prevent unwanted mirror activity (Duque et al. 2007; Hinder et al. 2010). As such, IHI is thought to play an important role in minimizing mirror activity (i.e., bilateral activity in homologous muscles in each limb) during movements which are intended to be unilateral. However, because direct interhemispheric connections of M1 are relatively sparse compared with those connections between areas upstream of the M1 (Carson 2005), task-specific alterations in transcallosal connections between areas upstream of M1 may play an important role in governing bimanual coordination. Indeed, a dominant role is thought to be played by the dorsolateral aspect of the right premotor cortex (rPMd) (Tanji et al. 1988), although cell recordings in monkeys do indicate that a population of cells within M1 is active during bimanual coordination (Donchin et al. 1998). Extant work has not, as yet, elucidated how those specific regions that are active during bimanual actions project or interact with each other, and how these task-related interactions may influence bimanual performance. The focus of this Neuro Forum is a recent report by Liuzzi et al. (2011) that provides interesting new data in this regard.

Liuzzi et al. (2011) assessed interhemispheric connectivity (rPMd to lM1; rM1 to lM1) during the preparation of ballistic (unimanual) right index finger abductions at various time points following presentation of a visual "go" signal, but prior to the onset of the volitional muscle response (Fig. 1*A*; also see Liuzzi et al. 2011, Fig. 2*A*). rPMd stimulation facilitated output from the lM1 throughout the preparation period, whereas rM1 stimulation had a substantial inhibitory influence on lM1 early in the preparation period, which became less strong (less inhibitory) close to the response, consistent with the idea that the impending action is released (Duque et al. 2007). In a separate behavioral protocol, participants were required to perform a number of bimanual and unimanual tapping tasks with the fingers of the right and left hands (Fig. 1*B*; also see Liuzzi et al. 2011, Fig. 1). Two "in-phase" bimanual tasks required participants to either simultaneously tap their index fingers on the first beat of a metronome, and then simultaneously tap their middle fingers on the subsequent beat, or to continually tap both index fingers simultaneously. The "anti-phase" bimanual task required simultaneous tapping of contralateral index and middle fingers. Numerous studies have shown that performing a bimanual motor task in which homologous muscle groups in contralateral limbs are activated simultaneously (in-phase) is intrinsically more stable than those tasks in which homologous muscle groups are required to be activated in anti-phase. Indeed, as the speed at which an anti-phase coordination pattern is performed increases, spontaneous transitions to the in-phase pattern can occur (see Swinnen 2002, for review). As such, Liuzzi et al. (2011) determined the level of performance of each participant in the anti-phase task as the frequency at which the transition from

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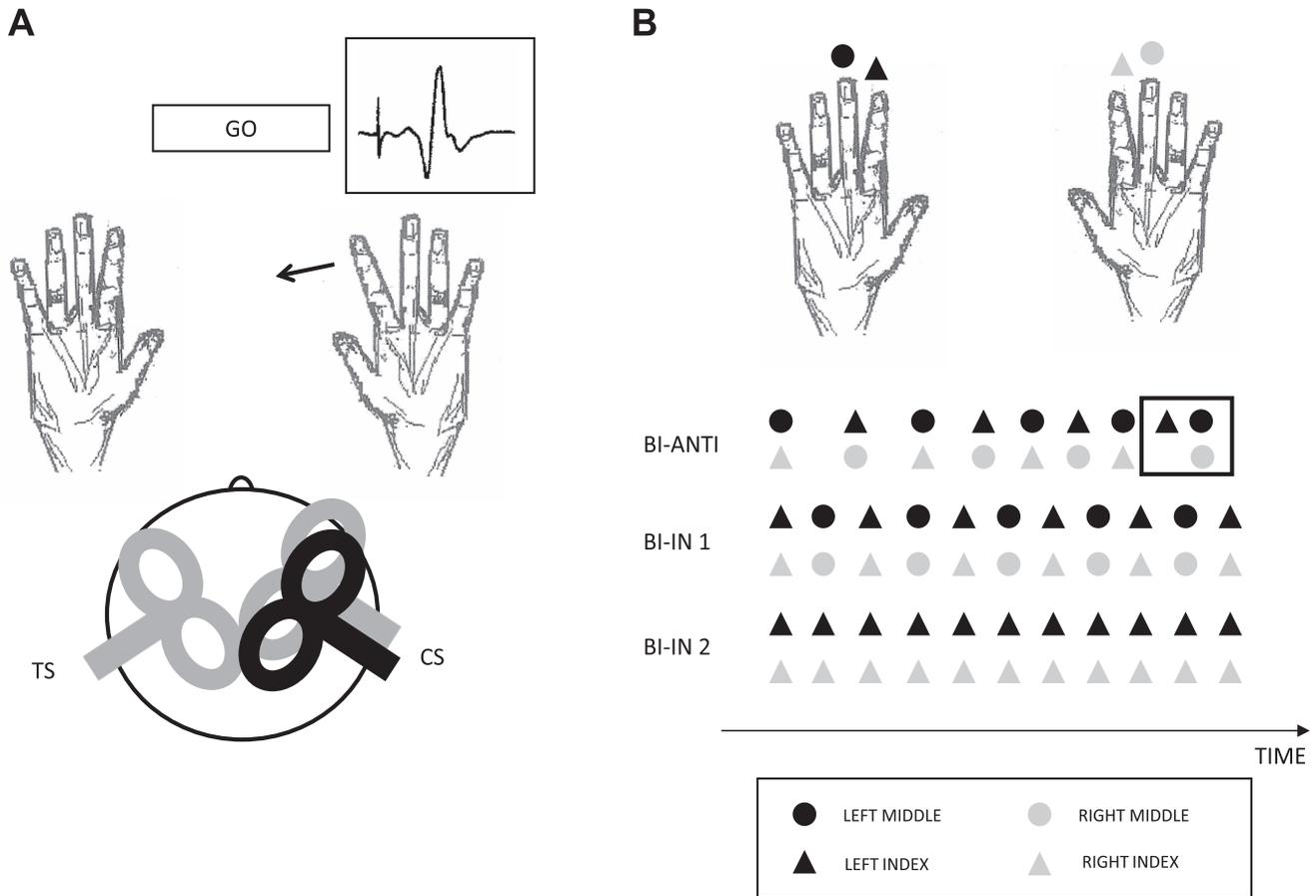
Fig. 1. *A*: interhemispheric connectivity was assessed using dual-coil transcranial magnetic stimulation (TMS) during the response period of a simple reaction time task. Participants were instructed to abduct their right index finger in response to a "go" signal. TMS was administered at 4 time points between the go signal and onset of muscle activity in the right index finger. The test stimulus (TS) was applied to the left motor cortex to elicit an evoked potential (MEP) in the right index finger. On 50% of trials, the TS was preceded by a conditioning stimulus (CS) applied to right motor cortex (black coil) or right dorsal premotor cortex (gray coil). The nature of the connectivity was assessed by determining how the MEP amplitude was affected by conditioning stimuli at the various time points. *B*: coordination tasks. Participants were instructed to tap 1 of 3 bimanual coordination patterns: BI-ANTI required simultaneous taps with the right index finger and left middle finger, followed on the next metronome beat by a simultaneous tap of the left index and right middle fingers. Performance was assessed as the metronome frequency prior to a spontaneous transition (see boxed region) to the in-phase pattern. Two in-phase patterns required fast-as-possible bimanual tapping with both index fingers followed by both middle fingers (BI-IN 1), or continuous bilateral tapping of both index fingers (BI-IN 2). The symbols in the tapping time lines are presented in the key (*bottom*).

anti-phase to in-phase coordination occurred. For the in-phase task, participants were instructed to tap the required pattern as fast as possible, and the level performance was determined as the mean number of taps during the trial.

Multiple regression analyses revealed that stronger facilitatory connections from rPMd to lM1 early in the preparation period were associated with improved performance in the anti-phase bimanual tapping task (Liuzzi et al. 2011, Fig. 2*B*). In contrast, less inhibitory influence from rM1 onto lM1 was associated with better performance in the in-phase bimanual tapping. This second result may have been predicted on the basis of the assumption that a release of inhibition between contralateral primary motor areas is required for simultaneous activation of homologous muscle groups in contralateral limbs. However, the correlation found provides an elegant quantitative assessment of this process. Overall, the findings highlight for the first time how the task-related connectivity between distinct motor areas may underlie skilled execution of rhythmic tapping sequences. However, undertaking a number of additional lines of inquiry to extend upon these initial findings appears necessary to fully understand the underlying

neural mechanisms and implications of the results with respect to movement control, rehabilitation, and clinical contexts.

As alluded to above, Liuzzi and colleagues (2011) measured interhemispheric connectivity from rPMd and rM1 onto the cortical representation of the right index finger (first dorsal interosseus; FDI) within the lM1 during the preparation of a fast as possible response (index finger abduction). The nature of these connections was then correlated with the ability to perform the in- or anti-phase bimanual tapping or unimanual tapping, conducted in a separate behavioral experiment. It therefore remains to be elucidated as to whether the modulation of interhemispheric connectivity observed during the preparation of the simple motor task would show similar characteristics (and be a prerequisite for accurate performance) during execution of the bimanual coordination tasks. An experiment in which task-related modulation of interhemispheric connectivity and task performance are assessed in situ, i.e., within the same (unimanual and bimanual) task, although technically more difficult, would shed more light on the role of task-related

modulation of connectivity for the specific control of both unimanual and bimanual actions.

Perhaps most intriguingly, the result of Liuzzi et al. (2011) suggests that interhemispheric connectivity of the right FDI (assessed during a simple reaction time task in which the FDI muscle was principally involved in movement execution) may predict the performance of a more complex tapping task requiring specifically timed phasic activation of both flexors and extensors of the first and second digits, on one or both hands. It is interesting to speculate, therefore, whether task-related changes in interhemispheric connectivity for the FDI (in simple reaction tasks) could also be used to predict performance in other bimanual tasks, perhaps involving motion across two joints and conceivably employing more proximal muscles, e.g., wrist extensors or forearm pronators/supinators, which replicate more closely those actions required in everyday tasks. If this was indeed the case, a simple laboratory (reaction time) task could conceivably be used to identify those individuals who may suffer from coordination problems in later life, when other age-related factors also contribute to deterioration of bimanual coordination. However, recent evidence suggests that specific brain areas are differently activated when both hands cooperate to undertake a unified goal (e.g., opening a jam jar lid, tying a shoelace) compared with when both hands are required to simultaneously undertake two independent tasks (Duque et al. 2010). Accordingly, speculating an association between interhemispheric connectivity and everyday tasks requiring coordinated actions of both hands on the basis of Liuzzi's results should be undertaken with some degree of caution. Furthermore, research reported in this journal (Harris-Love et al. 2007) has indicated that morphological and functional differences exist between proximal and distal muscles of the upper limb, with the transcallosal projections between the representations of distal limb muscles being less prominent than the projections between more proximal muscles. Consistent with these anatomical differences, IHI was shown to vary for various homologous muscle pairs depending, at least in part, on their proximal-distal location with respect to the (upper) limb (Harris-Love et al. 2007). As such, task-related changes in IHI in one muscle may not correlate with performance of tasks utilizing muscles with different transcallosal connectivity.

On the basis of the studies alluded to above (Duque et al. 2010; Harris-Love et al. 2007), experimental protocols that assess the relationship between interhemispheric connectivity task and performance during a standard lab-based bimanual task e.g., circling or tapping (employing finger, wrist and/or elbow joints), as well as during a more "ecological" or everyday bimanual task requiring multi-joint movements and a unified task goal (see Serrien et al. 2001; also Duque et al. 2010) would provide important additional knowledge. Given that noninvasive brain stimulation methods have the potential to "prime" interhemispheric circuitry as a treatment for movement disorders (see Liuzzi et al. 2011), it could be the case that (if associations between motor performance and interhemispheric connectivity were observed) similar priming could be used to alter interhemispheric connections with the aim of facilitating recovery following stroke or to offset functional losses of a limb immobilized due to fracture. Determining whether the findings of Liuzzi et al. generalize to enable "performance prediction" in everyday tasks, and specifically

those that utilize muscle groups that are primarily affected by stroke (e.g., the wrist extensors), is thus a crucial step if the current findings are to be exploited in a rehabilitation and clinical context.

As noted by Liuzzi et al. (2011), the current study does not provide evidence of a direct causal relationship between early modulation of rPMd-lM1 connectivity and performance in the anti-phase bimanual coordination task. While the specific relationship between PMd-M1 connectivity (and not M1-M1 connectivity) and bimanual anti-phase performance speak to a role or mechanism specific to the PMd, a valuable line of investigation would be to conduct a "virtual lesion" study. In an elegant study, Hübers et al. (2008) recently used this approach to provide evidence that the degree of IHI between the primary motor cortices is causally related to the degree of mirror activity observed during a simple motor task. In the proposed protocol, theta burst stimulation or repetitive TMS would be applied to the rM1, rPMd, or another non-motor region (as a control). The effect of the virtual lesion would be assessed in terms of neurophysiological (i.e., change in connectivity relative to connectivity assessed prior to the lesion) and behavioral (performance change in a coordination task) parameters. If the hypothesis suggested by Liuzzi and colleagues was indeed true, one would expect rPMd stimulation to affect rPMd-M1 connectivity and bimanual anti-phase performance, while rM1 stimulation may affect rM1-lM1 connectivity together with unimanual and bimanual in-phase performance.

In summary, the work of Liuzzi et al. (2011) builds on previous studies that have reported task-related modulation of connectivity between premotor and motor regions within (e.g., Byblow et al. 2007) or between (e.g., O'Shea et al. 2007) cortices by providing timely new evidence of an association between the nature of interhemispheric connectivity and bimanual motor performance. Further work is warranted to gain deeper insight into this relationship before it can potentially be utilized in clinical or therapeutic interventions to assist in motor recovery.

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