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Directionality of interhemispheric communication

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Introduction

Understanding anatomical and functional connectivity between different brain regions is key not only to our basic understanding of how the brain operates but also to the study of pathways for seizure propagation in patients with epilepsy. Thus, a vast literature concerning functional connectivity has arisen from the opportunistic observation of patients with intractable epilepsy, due to the facility to conduct invasive stimulation via depth electrodes implanted during surgery. However, can this method tell us anything about the directionality of transcallosal transfer of information?

In a series of investigations, Lacuey et al. (2015a, b; 2016) placed stereotactically implanted electrodes into cortical and subcortical brain regions as part of surgical evaluation for intractable epilepsy. They stimulated unilaterally through these electrodes, and observed whether cerebro-cerebral evoked responses (CCEPs) were elicited both ipsilateral and contralateral to the stimulation. In Lacuey et al. (2015b), the presence of bilateral responses in the hippocampus of two out of seven patients following unilateral fornix stimulation was taken as evidence of the existence of connections between bilateral mesial temporal structures. In an investigation of transcallosal connectivity between right and left anterior insula in one patient (Lacuey et al. 2016), they report bidirectional connectivity between homotopic anterior insula sites, with responses

appearing in the contralateral insula with latencies ranging from 8 to 24 ms. They use this information to confirm the existence of pathways that may allow seizure propagation between hemispheres.

According to a controversial theory outlined in Derakhshan (2005), the observation of bilateral responses to unilateral electrical stimulation should occur exclusively upon stimulation of the non-dominant side of the body. This has not been the case in other investigations, as bidirectional connectivity has been reported in right and left handers using CCEPs (Lacruz et al. 2007) and laser-evoked potentials (LEPs) (Frot and Mauguière 2003). Derakhshan states that the directionality of callosal traffic between homotopic regions in the motor system is exclusively from the dominant to the non-dominant hemisphere. This is the ‘one-way callosal traffic theory’, which surmises that the dominant limb has a direct connection to the brain’s ‘command center’ in the ‘major hemisphere’, while the non-dominant limb does not, requiring all movement commands and all sensations to be sent/received indirectly via callosal communication with the dominant hemisphere. As this requires the negotiation of additional synapses along the way, there is more random variability (and delays) in the transmission of these signals (and upon resulting behaviors, such as that measured by the bilateral simultaneous drawing task (Derakhshan 2008). In other work, Derakhshan et al. (2003) writes that “the doctrine of contralaterality of movement control (that is, the left hemisphere controls the right side of the body, whereas the right hemisphere controls the left) is a simplistic half-truth and is in need of modification if it is to become a scientific theory” (p410). In another article, he states that his own results provide evidence of lack of any motor communication from the minor to the major hemisphere (Derakhshan 2015).

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This is an evocative suggestion. The general idea that handedness emerges because the ‘dominant hemisphere’, is used to plan movements of both arms was in fact suggested over a century ago by Liepmann (1905). This suggestion has subsequently been supported by functional neuroimaging (e.g., Haaland and Harrington 1996) and remains relatively undisputed. However, to claim that the directionality of callosal traffic in the motor realm is exclusively from the major to the minor hemisphere, and to expect electrical stimulation studies to reflect this, appears to be at odds with evidence from a range of different sources and modalities.

The dynamic dominance model

An alternative theory that has gained substantial empirical evidence is the dynamic dominance model of handedness, which outlines that each hemisphere contributes unique features of control to each arm (Sainburg 2005). This has been supported by data indicating advantages of the non-dominant arm for specific aspects of control (Bagesteiro and Sainburg 2002, 2003; Duff and Sainburg 2007; Wang and Sainburg 2007). Specifically, the dynamic dominance hypothesis suggests that the dominant hemisphere has become specialized for controlling task dynamics, as required for coordinating efficient visually guided trajectories, whereas the non-dominant hemisphere has become specialized for controlling limb impedance, as required for achieving stable postures. Thus, findings relating to the directionality of callosal traffic are extremely task sensitive, and in certain situations bidirectional communication is essential.

Observations from stroke patients are also in accordance with the dynamic dominance model. Evidently, stroke-induced lesions in the sensorimotor system (regardless of hemisphere) result in hemiparesis in the contralesional limb, suggesting a crucial role for the contralateral hemisphere in movement execution. Interestingly, however, the ipsilesional limb often shows separate motor coordination deficits (Fisk and Goodale 1988; Haaland and Harrington 1989; Winstein and Pohl 1995; Haaland and Harrington 1996; Sunderland 2000; Yarosh et al. 2004; Wetter et al. 2005; Sainburg and Duff 2006; Schaefer et al. 2007). Importantly, these deficits seem to vary with the hemisphere that is lesioned, again suggesting that contributions from each hemisphere are lateralized (Schaefer et al. 2007).

Short-latency afferent inhibition

More evidence for bidirectional transcallosal traffic in the sensorimotor system comes from studies of short-latency afferent inhibition (SAI). This is the phenomenon where a brief electrical pulse of somatosensory stimulation applied

to one limb (typically fingertip or wrist) results in a short burst of inhibition in the contralateral primary motor cortex (M1) ~ 23 ms later (i.e., Exactly at the moment that the stimulation has reached the cortex) (Maertens de Noordhout et al. 1992; Tokimura et al. 2000). The inhibition is measured as reduced motor-evoked potential (MEP) amplitude in response to transcranial magnetic stimulation (TMS), and is considered an index of sensory-motor integration, as the stimulation pulse first reaches the primary sensory cortex (S1) before travelling intracortically to M1 to directly influence motor output. Importantly, ~ 15 to 18 ms later a similar bout of inhibition can be measured in the opposite M1, indicating transcallosal transfer of the signal. This has been termed ipsi-SAI (Conde et al. 2013), and occurs with similar latencies regardless of whether the dominant or non-dominant limb is stimulated (Ruddy et al. 2016a). This functional pathway allows bidirectional sensory-motor integration between hemispheres. If Derakhshan’s claim that all sensations from the non-dominant side must first pass through the dominant hemisphere were correct, this pattern of results could not be achieved.

Structural connectivity

It is also noteworthy that the structural connections between regions in the human motor system do not reflect large asymmetries between the two hemispheres, as would be expected if callosal traffic were exclusively unidirectional. In a post-mortem histological study in humans, White et al. (1997) documented that the preferred use of the right hand occurs without a gross lateral asymmetry in the primary sensory motor system. More recently, advances in diffusion-weighted imaging have allowed transcallosal motor white matter pathways to be reconstructed in vivo in humans, again providing evidence of a largely symmetrical organisation (Ruddy et al. 2017a). Unfortunately, however, this method is not capable of discerning the directionality of functional traffic in the reconstructed fibre tracts.

Cross-education

How could the ‘one-way callosal traffic theory’ be reconciled with the knowledge that when a skill is learned (or strength is gained) following training with one limb, a portion of the benefit transfers to the opposite, untrained limb, regardless of which side is trained? This phenomenon has been termed ‘cross-education’, and while the precise neural mechanisms of this performance transfer remain only partially understood (Ruddy and Carson 2013; Ruddy et al. 2016b), it is emerging that transcallosal communication between the supplementary motor area (SMA) in the right and left hemispheres plays a key role (Ruddy et al. 2017b). Cross-education occurs bidirectionally, albeit in a

very task-dependent manner, whereby certain motor tasks transfer better from dominant to non-dominant than non-dominant to dominant (Wang and Sainburg 2005, 2006; Wang et al. 2011; Aiken et al. 2015). Again, this is reminiscent of the idea of dynamic dominance, that both hemispheres are specialized to perform different aspects of motor control.

Electrical stimulation in epilepsy patients

Playing devils advocate that one may raise the question of whether this debate on ‘normal’ human brain connectivity should consider evidence from depth electrode studies in epilepsy patients at all when the only evidence available comes from the study of a small handful of individuals, who even in the Lacuey et al. papers in question were admittedly considered ‘rare’ cases in the epileptic community. In Lacuey et al. (2016) the single patient in question had left and right temporal onset EEG seizures and seizure semiology suggested a single symptomatogenic zone in the insulo-opercular region. Based on the observation of bilateral CCEP responses from unilateral anterior insula stimulation, they concluded that their results confirm bidirectional interconnections between both homotopic anterior insular structures, and are consistent with reports of seizure activity spread from ipsilateral to contralateral insula. As Almashaikhi et al. (2014) used a similar depth electrode approach in two patients and found no bilateral CCEP responses, it may be suggested that the patient in Lacuey et al. (2016) was an exception rather than the norm, and that the presence of the reported reciprocal connections between right and left insula may be pathological; the vehicle of seizure spread. In the absence of complementary evidence from neurologically healthy brains, it is impossible to come to the conclusion that this type of reciprocal functional connectivity is the norm.

Conclusion

In summary, as this debate is ongoing, it is clear that hemisphere dominance is something that should be made fully transparent in future electrical stimulation studies to demonstrate whether responses to unilateral stimulation are truly different depending on the side that is stimulated. Invasive direct electrical brain stimulation studies are useful to establish that anatomical connections exist, but from this modality one can only make assumptions regarding the functional traffic in the stimulated pathways in their natural context. On consideration of the evidence, it is difficult to subscribe to Derakhshan’s idea that callosal traffic in the motor system is exclusively unidirectional, and that this pattern would be reflected by evoked

responses to electrical stimulation. Bidirectional traffic between motor regions in the corpus callosum is essential for normal motor functioning, especially for the upper limbs that require a high degree of cooperation for complex movements. The key issue to emphasise is task dependency, as the functional dynamics of interhemispheric communication are different depending on the demands placed on the system, so focusing on only one particular style of task, or on the results of electrical stimulation in isolation, can never be sufficient to resolve this argument.

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