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## Inter-hemispheric inhibition sculpts the output of neural circuits by co-opting the two cerebral hemispheres

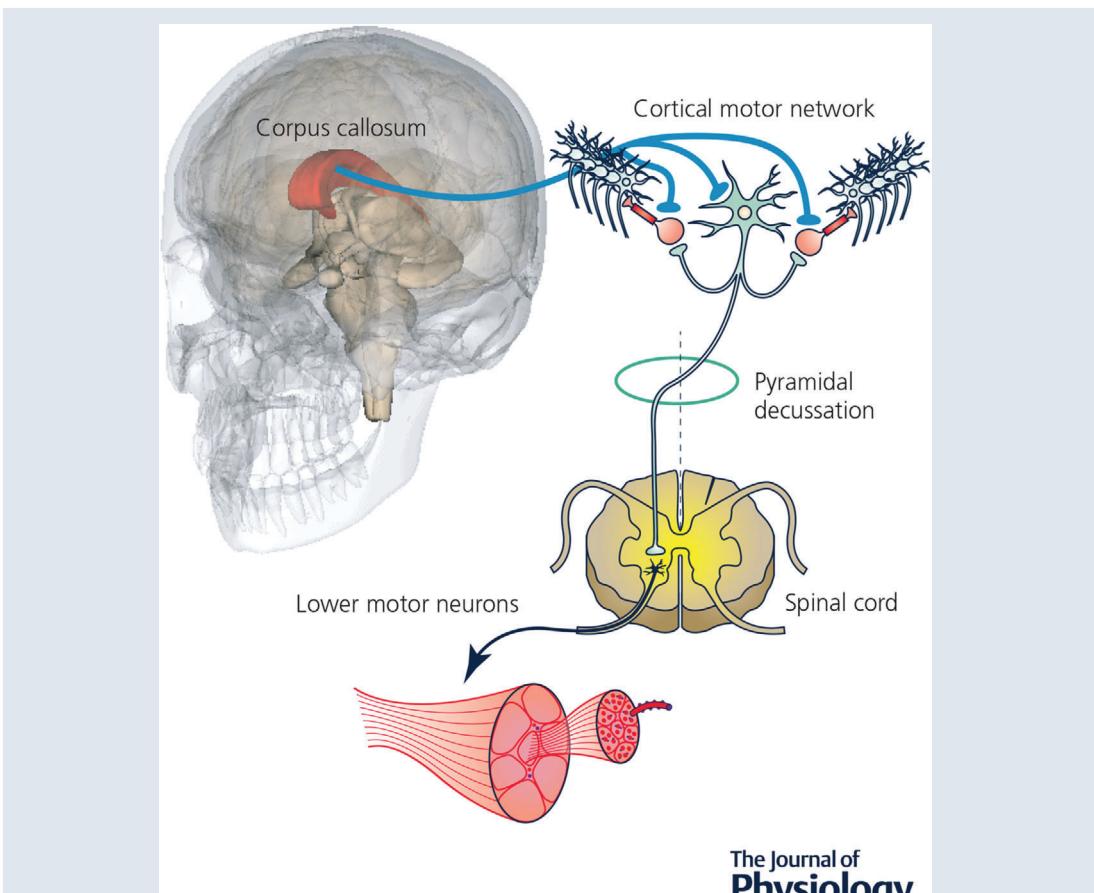
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**Abstract** ‘Inter-hemispheric inhibition’ is used frequently to describe the action of one hemisphere in suppressing or impeding processing in its counterpart. It is widely believed that this

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is required in order to prevent a bilateral cerebrum giving rise to simultaneous and potentially competing outputs. It is argued here that a fundamental role of inter-hemispheric inhibition is to support contrast enhancing and integrative functions by co-opting the capacities of the two cerebral hemispheres. Drawing upon an extensive body of empirical data, derived largely from animal models, and associated theoretical modelling, it is demonstrated that inter-hemispheric projections act via mechanisms such as surround/lateral inhibition. The principal functional unit of callosal influence comprises a facilitatory centre and a depressing peripheral zone, which together shape the influence of converging inputs to pyramidal neurons. Inter-hemispheric inhibition is an instance of a more general feature of mammalian neural systems, whereby inhibitory interneurons act not simply to prevent over-excitation but to sculpt the output of specific circuits. The narrowing of the excitatory focus that occurs through crossed surround inhibition is a highly conserved motif of transcallosal interactions in mammalian sensory and motor cortices. A case is presented that the 'inter-hemispheric competition' model has been sustained, and its clinical derivatives promoted, by erroneous assumptions concerning that revealed by investigative techniques such as transcranial magnetic stimulation (TMS). The alternative perspective offered here is also shown to be consistent with known associations between the structural integrity of callosal projections and the magnitude of the motor deficits that are exhibited following stroke.

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**Abstract figure legend** The principal functional unit of callosal influence comprises a facilitatory centre and a depressing peripheral zone, that together shape the influence of converging inputs to pyramidal neurons. This organization serves to sculpt and focus the output of neural circuits. In this schematic representation, cells that generate excitatory postsynaptic potentials (EPSPs) are represented in black. Callosal projections (excitatory) are represented in cyan. Inhibitory interneurons are represented in red. An inhibitory influence upon pyramidal tract cells in the surround region of the opposite hemisphere may arise from either local *feed-forward* inhibitory circuits or *recurrent* inhibitory circuits. Although the patterns of inhibition elicited by callosal projections are in part an emergent property of these local networks, the actuating excitatory drive (from the opposite hemisphere) is necessarily also selective and highly differentiated. A key assumption is that such inter-hemispheric interactions are reciprocal, and thus integrative. Figure redrawn and adapted from the author's original artwork, which is available at: [https://commons.wikimedia.org/wiki/File:Functional\\_unit\\_of\\_callosal\\_influence.jpg](https://commons.wikimedia.org/wiki/File:Functional_unit_of_callosal_influence.jpg) The original artwork contains elements derived from the following sources: [https://upload.wikimedia.org/wikipedia/commons/f/f3/Muscle\\_fascicles\\_and\\_cells.png](https://upload.wikimedia.org/wikipedia/commons/f/f3/Muscle_fascicles_and_cells.png); [https://commons.wikimedia.org/wiki/File:Corpus\\_callosum.gif](https://commons.wikimedia.org/wiki/File:Corpus_callosum.gif). All of the artwork was published under either a Creative Commons Attribution-Share Alike license or a Creative Commons CC0 Universal Public Domain Dedication.

## Introduction

The putative functions of inter-hemispheric (callosal) projections have informed the development of theories that deal with many aspects of the human condition, including hand preference (Witelson, 1985), consciousness (Sperry, 1976) and creativity (Bogen & Bogen, 1988), extending even to the defining characteristics of contemporary Western culture (McGilchrist, 2019). Particular emphasis has been placed on a notional role for these projections in giving effect to inter-hemispheric inhibition (e.g. Chiarello & Maxfield, 1996). It is widely believed that this is required in order to prevent a bilateral cerebrum giving rise to simultaneous and potentially conflicting outputs (e.g.

Moscovitch, 1976; Hellige, 1993). The central argument presented in the current review is that a fundamental role of inter-hemispheric inhibition is to support contrast enhancing and integrative functions by co-opting the capacities of the two cerebral hemispheres, rather than to permit suppression of one hemisphere by its counterpart.

In many areas of physiological enquiry, there is little direct practical effect, beyond impact on the rate at which basic knowledge is advanced, of debates that concern relationships between structure and function. When, however, the misrepresentation of these relations has a direct material bearing on the development and deployment of therapeutic interventions, the consequences may not be so benign. Conceptions of the roles assumed by callosal projections in mediating

inter-hemispheric inhibition provide a case in point. In this review, an analysis of motor impairments arising from stroke is used for two purposes. Firstly, the persistent failure of clinical interventions based on a specific model of functional relations between the cerebral hemispheres, that of mutual competition, is used to make the case that a fundamental reassessment of the underlying model is required. Secondly, the alternative conceptual framework that is developed, whereby inter-hemispheric inhibition acts to sculpt the output of neural circuits by co-opting the capacities of the two cerebral hemispheres, is shown to be consistent with known associations between the structural integrity of callosal projections and the magnitude of the motor deficits that are exhibited following stroke. Although emphasized by reference to impairments of motor control, the central arguments concerning the function of inter-hemispheric inhibition should be seen as applying more generally.

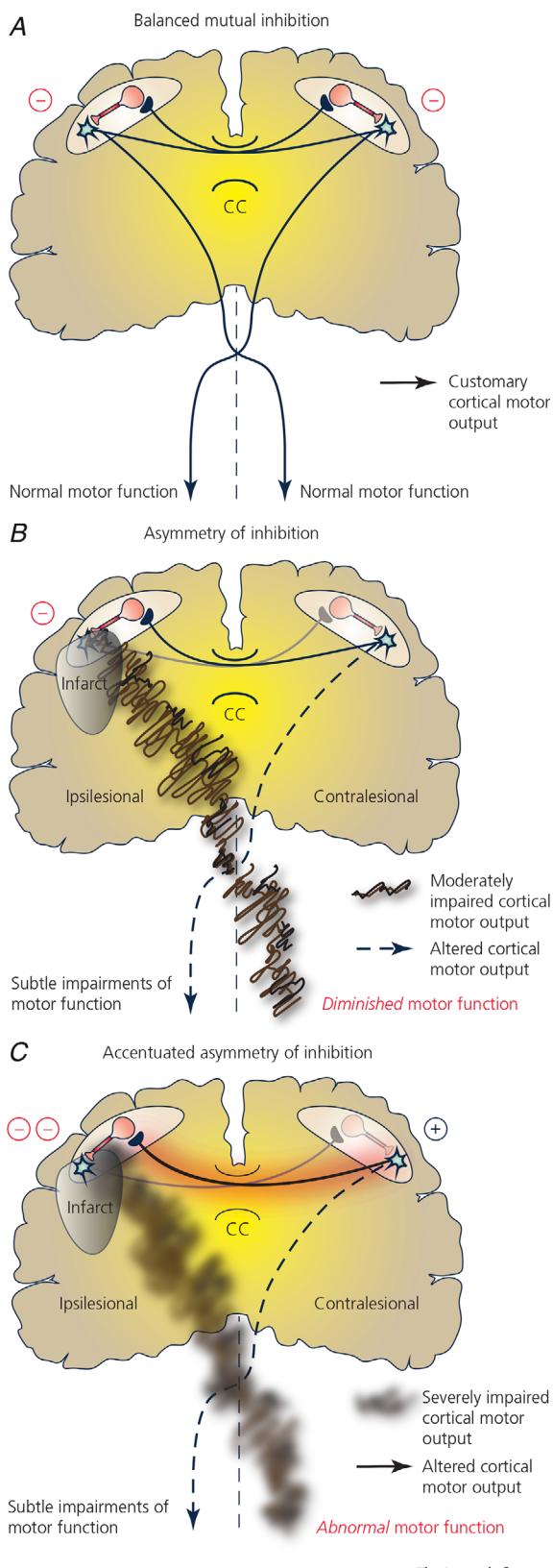
### The inter-hemispheric competition model

In seeking to deal cost-effectively with the burden of disability arising from stroke, national commissioning programmes have emphasized a requirement for new rehabilitation technologies and novel modes of therapy (e.g. Department of Health, 2007). In this context non-invasive brain stimulation (NIBS) has come to prominence. Among the various modalities of NIBS, transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have been investigated most extensively. It has been shown that in animal models, these forms of NIBS are capable of acting through a variety of cellular and molecular pathways that change gene activity and protein expression; alter inflammatory processes and oxidative stress; influence cell migration and orientation; regulate neurotransmitter and neurotrophin release; and promote neurogenesis and angiogenesis (for reviews see Pelletier & Cicchetti, 2015; Cirillo *et al.* 2017). When used in humans with the intent of ameliorating the impact of stroke, TMS and tDCS are typically applied with a view to altering cortical excitability, via the generation of action potentials or changes in resting membrane potential. This approach, in which the objective is typically to increase the excitability of neural circuits in the ipsilesional hemisphere, and/or decrease the excitability of circuits in the contralateral hemisphere, is predicated upon a specific conception of how the two sides of the brain interact. This has become known as the inter-hemispheric competition model.

At the core of this model is the assumption that during the generation of voluntary movement by one arm, there is inhibition of motor centres that give rise to efferent projections onto motoneurons innervating the homologous muscles of the opposite limb (e.g. Netz *et al.*

1995; Kobayashi *et al.* 2003; Duque *et al.* 2005). In referring to this assumption, the term 'inter-hemispheric inhibition' is typically used. This has been defined as an 'influence exerted by one hemisphere to suppress or impede processing within the opposite hemisphere' (Chiarello & Maxfield, 1996, p. 82). The interpretation is functional. That is, it does not necessarily imply a reduction in neural activity in the contralateral hemisphere (Bloom & Hynd, 2005; Chiarello & Maxfield, 1996). Nonetheless, the presence of inhibitory interneurons innervated by fibres with cell bodies located in the opposite hemisphere (i.e. an anatomical/physiological observation) is often interpreted as providing support for the (functionally defined) inter-hemispheric competition model. Conversely, the mere existence of such interneurons has frequently been the prism through which functional interactions between the hemispheres have been viewed. As will be demonstrated in the course of the present review, it does not follow from the actuality of synaptic inhibition invoked by fibres projecting from the opposite hemisphere that there is mutual competition between the cerebral hemispheres.

Although an interceding role of other pathways has not been precluded (e.g. Innocenti *et al.* 2017), the consensus view has always been that the fibres of the corpus callosum mediate inter-hemispheric inhibition (Meyer *et al.* 1995). In the context of the inter-hemispheric competition model, it is widely believed that damage to one cerebral hemisphere as a consequence of stroke leads to a reduction of inter-hemispheric inhibition from the damaged to the non-damaged hemisphere (Fig. 1). As a corollary, the excitability of the non-lesioned hemisphere is thought to increase, i.e. following release from inhibition by its counterpart. It is held that elevated excitability of the non-damaged side of the brain in turn brings about greater (inter-hemispheric) inhibition of the damaged side (Murase *et al.* 2004). Since it is assumed that this would have an adverse influence upon recovery of motor capability, the inter-hemispheric competition model has provided an impetus for the development of interventions for which the intent is to 'rebalance' the hemispheres (Fig. 2). As there exist specific forms of NIBS that have been shown to either increase or decrease the excitability of circuits within the primary motor cortex in healthy brains, it has been proposed that if applied to reduce an imbalance of excitability between the hemispheres, they may provide a basis for stroke therapy (Boddington & Reynolds, 2017). In seeking to reappraise the function of inter-hemispheric inhibition, it is instructive to consider the level of success that has been achieved using interventions predicated on the conception of an 'inter-hemispheric imbalance' – in particular those that have aimed to reduce inhibitory drive from the undamaged hemisphere to the damaged hemisphere.



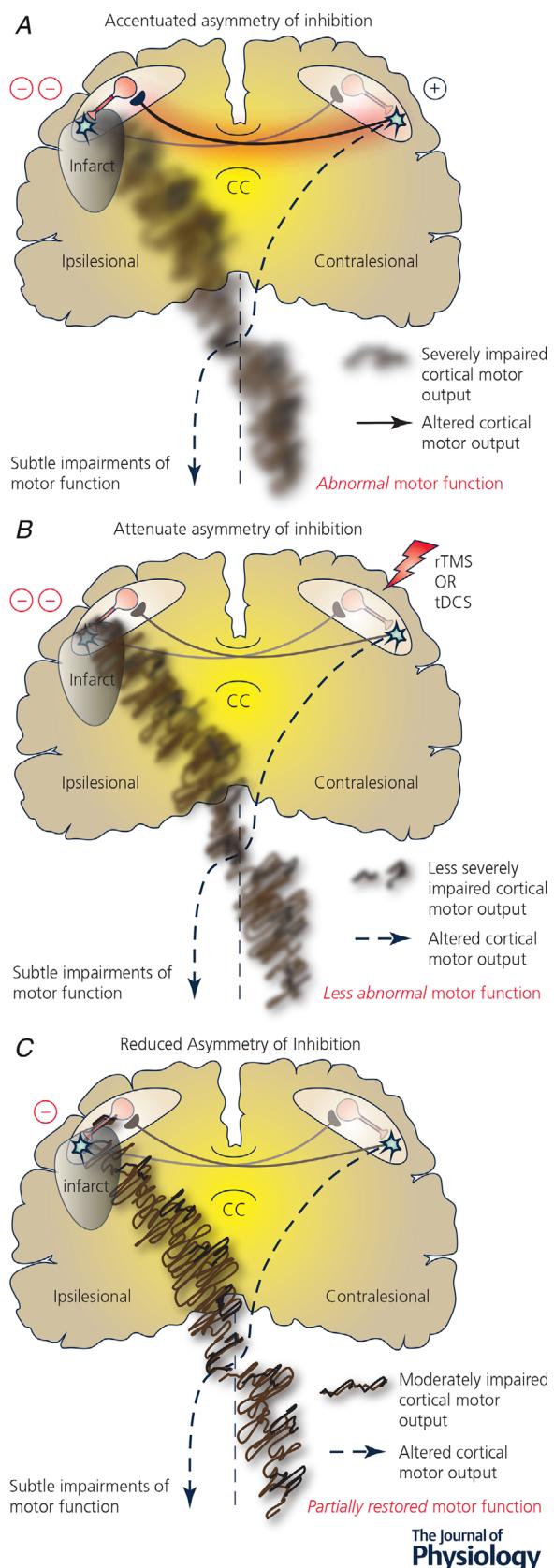
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## Effectiveness of interventions based on the inter-hemispheric competition model

As there has been a steady accumulation of randomized controlled trials in which various forms of NIBS have been applied with the intent of decreasing the excitability of circuits in the contralesional primary motor cortex (M1), it has become feasible to undertake meta-analyses of the clinical outcomes. The forms of repetitive TMS (rTMS) examined most frequently in this context have been those in which either 1 Hz trains (usually 1200–2400 stimuli in each application), or the ‘continuous’ variant of theta burst stimulation (usually 600 stimuli in each application), have been applied. The meta-analyses reveal that, when compared to task-specific training alone, there is no additional benefit of 1 Hz rTMS applied over the contralesional M1 on upper limb impairment (Valkenborghs *et al.* 2019). A similar conclusion may be drawn on the basis of studies in which the lower limb has been the focus of attention (Tung *et al.* 2019). Even when considered relative to a sham stimulation control, rather than to usual therapy, there is little evidence of a positive effect of (inhibitory) continuous theta burst stimulation on measures of upper limb function (Zhang *et al.* 2017). Corresponding meta-analyses have been undertaken to quantify the effect of cathodal tDCS, delivered with the objective of decreasing the excitability of contralesional

**Figure 1.** A schematic representation of the inter-hemispheric competition model, as it has been used to account for motor deficits resulting from stroke

A, illustration of the assumption that in the healthy brain there is balanced mutual inhibition between motor centres that give rise to efferent projections onto motoneurons innervating the homologous muscles of the opposite limb. B, illustration of the assumption that damage to one cerebral hemisphere as a consequence of stroke leads to a reduction of inter-hemispheric inhibition from the damaged to the non-damaged hemisphere. C, illustration of the assumption that there is, as a result, elevated excitability of the non-damaged side of the brain that brings about greater (inter-hemispheric) inhibition of the damaged side. It is emphasized that B and C represent physiological states that are not necessarily separable in time. The key shows the symbols used to represent the presumed characteristics of the cortical motor output associated with each state. In an abstract sense, these might be conceived of in terms of spatial and/or temporal ‘noise’. Although any such characteristics should not be regarded as strictly prescriptive, they may account for the abnormal patterns of muscle activation, including low specificity and high levels of muscle co-contraction, exhibited by stroke survivors (e.g. Dewald *et al.* 1995). Plausible corresponding effects on general motor function are given in the lower portion of each panel. It should be noted that the inter-hemispheric competition model does not typically encompass the bilateral deficits in motor control (shown here) that are observed frequently following unilateral brain injury (e.g. Desrosiers *et al.* 1996). The author’s original artwork is available at: [https://commons.wikimedia.org/wiki/File:Inter-hemispheric\\_competition\\_model.jpg](https://commons.wikimedia.org/wiki/File:Inter-hemispheric_competition_model.jpg) It was published under a Creative Commons Attribution-Share Alike 4.0 International license.



M1, prior to or during motor training. These analyses have likewise failed to produce evidence that the addition of cathodal tDCS generates clinical outcomes superior to those achieved through rehabilitation training alone (Triccas *et al.* 2016; Backhaus *et al.* 2018). Indeed, even when compared only to sham stimulation, there is no demonstrable benefit of cathodal tDCS in terms of clinical measures of upper (Elsner *et al.* 2016, 2017) or lower extremity function (Elsner *et al.* 2016). It is also apparent that with respect to rTMS in particular, and non-invasive brain stimulation in general, the results included in most meta-analyses exhibit a prior ‘significance bias’, such that the true effect sizes are likely to be very much smaller than those suggested by this method of aggregation (Amad *et al.* 2019). This inference is corroborated by the outcomes of an adequately powered multi-centre randomized controlled trial (~200 participants) in which 15 min of 1 Hz rTMS (or sham rTMS) was delivered to the contralesional M1, prior to each of 18 sessions of rehabilitation therapy undertaken during an intervention period of 6 weeks. There were no differences between the rTMS and the sham groups with respect to any clinical measure of upper limb impairment or function, either immediately after the intervention period or during the 6 months following (Harvey *et al.* 2018). The more general conclusion to be drawn is that interventions delivered with the intent of inhibiting the contralesional M1, whether by means of rTMS or cathodal tDCS, do not have clinical

**Figure 2. A schematic depiction of what is presumed to be the consequence of applying non-invasive brain stimulation (NIBS) with the intent of decreasing the excitability of circuits in the contralateral motor cortex**

*A*, the notional asymmetry of inter-hemispheric inhibition that is believed to arise as a consequence of a unilateral infarct caused by stroke. *B*, NIBS applied with the intent of decreasing the excitability of circuits in the contralesional motor cortex. The forms of NIBS applied most frequently in this context are repetitive transcranial magnetic stimulation (rTMS) and cathodal transcranial direct current stimulation (tDCS). *C*, the assumption that these forms of stimulation have the potential to decrease inhibition of the lesioned hemisphere by the non-lesioned hemisphere, and as a consequence reduce the net inhibition of motor centres that give rise to efferent projections to the paretic limb. It is emphasized that *B* and *C* represent physiological states that are not necessarily separable in time. The key shows the symbols used to represent the presumed characteristics of the cortical motor output associated with each state. In an abstract sense, these might be conceived of in terms of spatial and/or temporal ‘noise’. Plausible corresponding effects on general motor function are given in the lower portion of each panel. It should be noted that the potential impact of such interventions upon the bilateral character of deficits in motor control (shown here) that are observed frequently following unilateral brain injury (e.g. Desrosiers *et al.* 1996) is not usually considered. The author’s original artwork is available at: [https://commons.wikimedia.org/wiki/File:Rebalance\\_inter-hemispheric\\_inhibition\\_model.jpg](https://commons.wikimedia.org/wiki/File:Rebalance_inter-hemispheric_inhibition_model.jpg) It was published under a Creative Commons Attribution-Share Alike 4.0 International license.

utility in the context of movement rehabilitation following stroke (e.g. Nicolo *et al.* 2018).

As there is little evidence that decreasing the excitability of circuits in the contralesional M1 has a positive impact upon clinical outcomes, it is germane to consider the nature of the experimental studies that provided the foundation for this approach. In an influential investigation, Murase and colleagues (2004) reported that during the period immediately preceding the initiation of index finger movement, there was an inhibitory influence of the intact M1 on the lesioned M1 (in chronic survivors of subcortical stroke) that was in contrast to the facilitation seen in controls. It was also reported that the depth of the inhibition was correlated with assessments on the Medical Research Council (MRC) scale for muscle power. The key predictive measure was a paired pulse TMS elicited phenomenon that has also come to be known as ‘inter-hemispheric inhibition’ (IHI). It refers to the decrease in the magnitude of a ‘test’ motor evoked potential (MEP) that is obtained in response to stimulation delivered over M1, in circumstances in which an initial ‘conditioning’ stimulus has been applied 6–15 ms previously to the opposite M1 (Ferbert *et al.* 1992). Hereafter in this paper, ‘inter-hemispheric inhibition’ is used to refer to a physiological process, and ‘IHI’ to refer to this electrophysiological phenomenon. There also exists a long latency (LIHI) variant that is elicited using inter-stimulus intervals (ISIs) in the region of 50 ms. Another such experimental index is provided by the ipsilateral silent period (ISP). This is elicited when TMS is delivered at high intensity to the M1 ipsilateral to contracting muscles (Wassermann *et al.* 1991). These measures have in common that the magnitude of the effect (i.e. the notional depth of inhibition) increases with the intensity of the conditioning stimulus, and with muscle contractions performed by the limb contralateral to the site of the CS (for a fixed CS intensity) (Perez & Cohen, 2008; Chiou *et al.* 2013). Numerous studies with similar objectives to those of the Murase *et al.* (2004) have been conducted including several that employed either the LIHI (e.g. Kirton *et al.* 2010) or the ISP measure (e.g. Takechi *et al.* 2014). Frequently the stated conclusions are aligned with the view that many stroke survivors exhibit elevated inter-hemispheric inhibitory drive from M1 in the non-damaged hemisphere to M1 in the damaged hemisphere (Ward & Cohen, 2004). In the following section, consideration is given to whether the inferences made on the basis of such assertions are (1) conceptually valid and (2) in accord with the accumulated empirical evidence.

## Reassessing the inter-hemispheric competition model

It might first be determined whether there are logical deficiencies in the reasoning used to justify inter-

ventions undertaken with the aim of rebalancing excitability between the hemispheres, and by this means seeking to promote recovery of function. An important consideration is that a change in IHI over time that correlates with clinical measures, variation in expression of IHI across individuals that correlates with variation in clinical presentation, or an intervention that gives rise both to a change in IHI and a change in clinical status cannot be taken to indicate that there is a causal relationship between IHI and behavioural status (see also Bestmann & Krakauer, 2015; Xu *et al.* 2019).

A further critical issue is that IHI, LIHI and the ISP are electrophysiological phenomena that bear indirect relationships to multiple neurophysiological processes. Perhaps due to the (with hindsight unfortunate and ultimately confusing) adoption of the term ‘inter-hemispheric inhibition’ (IHI) to denote a particular TMS technique, the discourse is frequently such as to suggest that IHI provides a direct index of a physiological process with which it shares the name. This is representative of a widespread, and often unwarranted, dependence on TMS-derived measures in formulating more general statements concerning motor physiology (Carson *et al.* 2016). The reality is that the elicitation of all of these measures is such that they are relatively blind to, and indeed may mask, the expression of certain key physiological processes (Bestmann & Krakauer, 2015). This is a matter to which further consideration will be given in the sections that follow.

Even if TMS-derived measures are taken at face value, a damning indictment of the assumptions upon which interventions to rebalance the excitability of the cerebral hemispheres have been based is provided by the empirical data. In the context of a large-scale meta-analysis, McDonnell and Stinear (2017) reported that regardless of the TMS measure that was employed (IHI or ISP), there was no evidence of an imbalance between the hemispheres, when this was assessed in either acute or chronic stroke survivors. In other words, inhibition of the stroke-affected hemisphere by the non-affected hemisphere, as assayed by TMS, was not different from inhibition of the non-affected hemisphere by the affected hemisphere.

## Is there inhibition of homologous motor centres during voluntary movement?

A vital point to be made in the present context is that during movements that are unilateral by intention, there is net facilitation, rather than net inhibition, of neural pathways projecting to homologous muscles of the opposite limb. If there is one task for which TMS is relatively well suited, it is in reflecting the incidence of variations in the state of short- and long-range projections onto large-diameter corticospinal neurons with fast-conducting axons, which have cell bodies within

M1 and innervate motoneurons in the spinal cord (Lemon *et al.* 2002). In circumstances in which either direct or indirect activation of such pyramidal tract neurons by TMS results in a descending corticospinal volley that gives rise to depolarization of spinal motoneurons, this can be registered as a MEP. Since unilateral contractions increase the amplitude of MEPs evoked in the opposite limb (Hess *et al.* 1986; Stedman *et al.* 1998; Muellbacher *et al.* 2000), it can be inferred that unilateral actions induce bilateral elevations in corticospinal excitability (see Carson, 2005). This has been termed ‘crossed facilitation’. If the evoked response is elicited by (electrical) stimulation at the level of the cervico-medullary junction (rather than by TMS over the primary motor cortex), corresponding changes in response amplitude are not necessarily obtained (Hortobágyi *et al.* 2003; Carson *et al.* 2004). This suggests that the changes in corticospinal excitability arise principally from alterations in the state of circuits within the cortex, rather than at the level of the spinal cord.

It can also be seen that the amplitudes of potentials evoked by TMS in quiescent muscles of a static limb increase with the level of tension generated by the corresponding muscle on the other side of the body (Hortobágyi *et al.* 2003; Perez & Cohen, 2008, 2009; Sunday & Perez, 2012). During oscillatory movements, the MEP is potentiated to the greatest degree during the phase of motion during which the homologous muscle of the opposite limb is maximally engaged (Carson *et al.* 1999, 2004; Stinear & Byblow, 2002). MEPs are potentiated in the period preceding the initiation of a movement by the opposite limb. This increase in the excitability of corticospinal projections from the ipsilateral (i.e. to the movement) M1 reflects the specific muscles that are engaged rather than the direction of the movement in space (Chye *et al.* 2018).

In short, the empirical evidence indicates emphatically that during movement of the upper limb, there is net facilitation, *rather than inhibition*, of motor centres that give rise to efferent projections onto motoneurons innervating the homologous muscles of the opposite limb. The most obvious conclusion to be drawn is therefore that a notional state of affairs whereby there is inhibition of one hemisphere by its counterpart does not prevail. A more general question is whether, from a phylogenetic perspective, the presence of such ‘crossed facilitation’ is adaptive.

### **What is the nature of the problem to which inter-hemispheric inhibition supposedly provides the solution?**

In seeking to account for the crossed facilitation that occurs during unilateral actions, it has been

suggested that the phenomenon reflects a phylogenetically ancient organization of the motor system that promotes symmetrical bilateral movements (e.g. Hopf *et al.* 1974). If there is a predisposition of this nature, its expression does not appear to be mediated by direct anatomical connections between the cortical regions from which project the majority of fast-conducting corticospinal axons that innervate spinal motoneurons. Indeed, the sparse nature of the (direct callosal) projections between left and right caudal M1 in Old World monkeys and in humans (which may be designated posterior M1 (M1p) in histological atlases of the human brain) appears to represent one facet of a more recently evolved organization of motor cortex that supports fractionated movements of the digits and independent control of the hands (Rouiller *et al.* 1994; Wiesendanger *et al.* 1994). Since there is little scope (i.e. in terms of a material substrate) for direct facilitatory interactions between the left and right caudal portions of M1 (Dancause *et al.* 2015; Ruddy *et al.* 2017), by the same token, there is no obvious means by which direct inter-hemispheric inhibition between these specific areas can be instantiated. In other words, the term ‘last-stage inhibition’ (Cincotta & Ziemann, 2008) does not apply. But what is the nature of the problem to which inter-hemispheric inhibition supposedly provides the solution?

In 1985, MacKenzie and Marteniuk noted that there is no complete taxonomy of bimanual coordination tasks (MacKenzie & Marteniuk, 1985). Notwithstanding classification of bimanual tasks for the purpose of defining post-stroke treatment targets (Kantak *et al.* 2017), more than a quarter of a century later this remains the case. There is, however, a degree of consensus in relation to their defining features. Cooperative goal-directed actions performed by the two hands are considered emblematic of many uniquely human skills. Often in such tasks there is a clear differentiation of roles. Characteristically, the so-called ‘non-dominant’ limb (i.e. the left in right-handed individuals) performs a postural role, whereas the ‘dominant’ limb acts upon or manipulates objects. In some cases the non-dominant hand provides a positional reference for the manipulative hand (Wiesendanger *et al.* 1994). The demarcations extend to motor skills for which many years of intensive practice are required to achieve mastery (Ericsson *et al.* 1993). For example, in playing the violin the dominant hand wields the bow; the non-dominant hand provides support and executes the fingering. When framed simply in terms of the goal of a task, such as strumming a chord on the guitar, the clear differentiation of roles accorded to the two hands at first glance implies that any intrinsic tendency towards symmetry of simultaneous movements must necessarily have been suppressed. What descriptions at this level of analysis fail to reveal is temporal segmentation. The picture that emerges from

detailed observation is that the CNS formulates a single chain of timed commands in the context of which constituent movements are interleaved (Peters, 1977). Even for highly accomplished musicians, departure from a common time base (i.e. for the two hands) presents almost insurmountable difficulties (Peters, 1985). In short, for most cooperative goal directed actions in which the hands play differentiated roles, movements (transitions between postures) are sequential rather than simultaneous. When the two hands do perform movements simultaneously, the pervasive tendency is for these to be symmetrical.

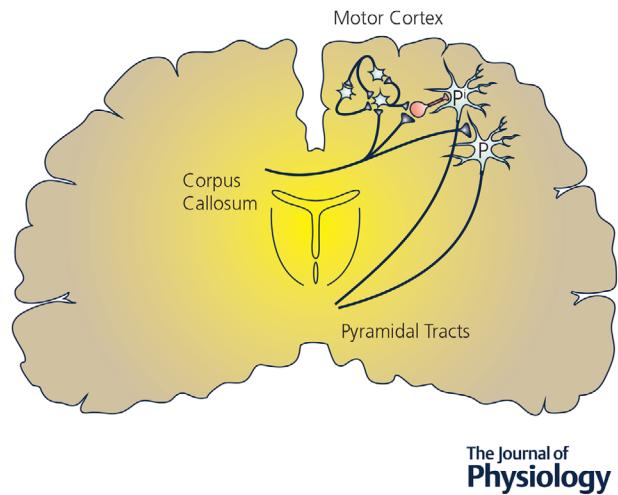
This can be illustrated in many ways. In unimanual, target-directed aiming tasks, the size of the target and the distance of the target from the starting position predict movement duration in a fashion that is described well by Fitts's law (Fitts & Peterson, 1964). If both hands are moved to separate targets for which Fitts's law predicts distinct durations, the hands nonetheless start and end movement in close temporal proximity to one another (Kelso et al. 1979a,b; Marteniuk *et al.* 1984; Riek *et al.* 2003). The disposition towards symmetrical simultaneous movement is also readily revealed by continuous/repetitive tasks, particularly when their rate of execution reduces the time available for the CNS to interleave limb-specific sequences of motor commands. When asked to repeatedly draw circles with one hand and vertical lines with the other, spatial coupling occurs, whereby the trajectory of each limb adopts the features of the other (Franz *et al.* 1991). Patterns of bimanual coordination in which homologous muscles are engaged in an alternating fashion cannot be performed in a stable fashion, particularly as the frequency of movement is increased. In contrast, patterns in which homologous muscles are active simultaneously, and the movements therefore symmetrical, typically remain stable to the point at which the frequency of movement can no longer be increased (Cohen, 1971; Kelso, 1984; Riek *et al.* 1992). In the course of performing the tasks of daily living, such spatial and temporal coupling may be transient (Heuer, 1993), and often not readily perceived or observed. The tendency for simultaneous symmetrical movement is nonetheless ubiquitous (Swinnen, 2002). This is the context in which the functional role of inter-hemispheric inhibition must be assessed, rather than in some notional state in which synchronous bilateral activity is suppressed – a state that the CNS manifestly does not achieve.

### The concept of surround inhibition

It is a central tenet of the inter-hemispheric competition model that movements of one arm are accompanied by the inhibition of motor centres with projections onto motoneurons innervating the homologous muscles of the opposite limb. It is clear, however, that this is not what occurs. In normal physiological conditions, there is in fact

a high degree of bilateral coupling not only between brain centres linked most directly to efferent projections, but also within the somatosensory network (e.g. Dietz *et al.* 2015). There is thus a need to consider the functional role that is played by inter-hemispheric inhibition in the context of such coupling, rather than persisting with the view that it is somehow necessary in order to oppose the 'default' state. From a broader phylogenetic perspective, it is difficult to discern circumstances in which a system would have evolved to modulate excitation in such a manner that a counteracting layer of inhibition must then be superimposed. The alternative considered here is that inter-hemispheric inhibition is an instance of a more general feature of mammalian neural systems, whereby inhibitory interneurons act not simply to prevent over-excitation but to sculpt the overall output of specific circuits (Merchant & Georgopoulos, 2017).

Experiments in cat reveal the presence of facilitatory connections with the homotopic area of the opposite motor cortex, which are surrounded by a more extensive zone in which inhibitory responses to transcallosal stimulation are obtained (Asanuma & Okuda, 1962; see Fig. 3). The wider dispersion of inter-spike intervals, registered by single unit recordings, suggests that there



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**Figure 3.** Author's rendition of Asanuma and Okuda (1962, Fig. 9), representing the manner in which callosal projections from one hemisphere give rise to an excitatory influence upon pyramidal tract cells in a restricted area, and an inhibitory influence upon pyramidal tract cells in the surrounding region of the opposite hemisphere

Cells that generate excitatory postsynaptic potentials (EPSPs) are shown in black. The red cell is an inhibitory interneuron. The pyramidal cell labelled P is subject to excitatory drive. The pyramidal cell labelled Pi lies within the peripheral inhibitory zone. Asanuma and Okuda assumed that a 're-exciting interneuronal chain' permits the interneurons to fire repetitively. The author's original artwork is available at: [https://commons.wikimedia.org/wiki/File:After\\_Asanuma\\_%26\\_Okuda\\_1962\\_Fig9.jpg](https://commons.wikimedia.org/wiki/File:After_Asanuma_%26_Okuda_1962_Fig9.jpg) It was published under a Creative Commons Attribution-Share Alike 4.0 International license.

are a greater number of interceding synaptic relays in the peripheral (inhibitory) zone (Kogan & Kuraev, 1976). This accords with the consensus view that callosal neurons are typically glutamatergic (Innocenti, 1986; Werhahn *et al.* 1999) and exert a facilitatory influence upon their immediate targets in the opposite hemisphere (Voigt *et al.* 1988; Conti & Manzoni, 1994; Houzel & Milleret, 1999). Although callosal fibres arising from GABAergic cells have in some case been identified (e.g. Gonchar *et al.* 1995; Fabri & Manzoni 2004; Rock *et al.* 2018), for the most part the inhibitory responses arise from neural interactions that occur within circuits local to the opposite hemisphere (Bianki & Shrammapril, 1985; Berlucchi *et al.* 1990; Daskalakis *et al.* 2002; Carson, 2005). Only a small fraction of callosal inputs onto pyramidal cells are, however, subject to GABAergic (i.e. inhibitory) modulation (Carr & Sesack, 1998). This is consistent with indications that between 5% and 20% of long-distance extrinsic connections within cortex synapse onto inhibitory cells (Fisken *et al.* 1975; McGuire *et al.* 1991). More pertinently one might ask: what purpose do local inhibitory effects brought about by callosal input serve?

The organization described by Asanuma and Okuda bears some of the hallmarks of lateral/surround inhibition (Hartline & Ratliff, 1972), a fundamental characteristic of neuronal processing. Barlow (1953) described surround inhibition in studies of ganglion cells in the frog retina. He noted that the inhibitory action of light falling outside the receptive field of receptor cells exerts a discriminatory action on the response profile of the ganglion cells to which they project, which serves to increase the degree of contrast sensitivity that can be achieved. As Barlow concludes (p. 87), a system configured along these lines acts as a filter, ‘rejecting unwanted information and passing useful information’.

It was established subsequently that this form of organization is omnipresent in sensory processing systems. For example, within the posterior column medial lemniscal system (PCMLS), surround inhibition is operative initially within the posterior column nuclei, and remains evident in all relays of the PCMLS. By this means the discrimination of stimuli applied to separate points on the skin is sharpened and enhanced – a facility necessary for capabilities such as two-point discrimination. Surround inhibition is also thought to play a significant role in sharpening the orientation selectivity of cells in primary visual cortex (V1) (Shapley *et al.* 2003). The columnar arrangement found in the cerebral cortex assumes particular functional significance in this regard (Mountcastle, 1957), supporting orderly patterns of connectivity that, through surround inhibition, not only focus but also amplify sensory input (Eccles, 1971).

Although historically the thesis has been subject to less extensive empirical scrutiny (e.g. Stefanis & Jasper, 1964a,b), Eccles (1971) pointed out that the amplification

and sharpening of neuronal activity realized by surround inhibition also assumes a key role in shaping motor output. This idea has been developed recently by Georgopoulos and colleagues, in a series of papers (Merchant *et al.* 2008; Georgopoulos & Stefanis, 2010) outlining the proposition that these local inhibitory mechanisms are critical for controlling the directional accuracy and speed of reaching movements (Mahan & Georgopoulos, 2013) (Fig. 4). The observation that the local circuit mechanisms that influence the coding of movement in the motor cortex are in some cases similar in character to Renshaw inhibition (for review see Hultborn *et al.* 1979) in the spinal cord (Stefanis & Jasper, 1964b; Kameda *et al.* 1969; Georgopoulos & Carpenter, 2015) serves to emphasize that, as with its sensory counterpart, surround inhibition is a ubiquitous feature of the motor system.

Following Bianki (e.g. Bianki & Makarova, 1980; Bianki, 1981; Bianki & Shrammapril, 1985), we have proposed previously (Ruddy & Carson, 2013) that the organization first described by Asanuma and Okuda (1962), excitation by stimulation of an approximately symmetrical point in the opposite M1 cortex and inhibition by stimulation of the immediately surrounding area, provides for the sharpening of movement-related neuronal activity through crossed surround inhibition. Although callosal fibres may innervate both pyramidal cells and inhibitory interneurons (e.g. Carr & Sesack, 1998; Karayannidis *et al.* 2007), it is significant that the (GABAergic) cells mediating transcallosal (usually disynaptic) inhibitory postsynaptic potentials (IPSPs) can be driven by axon collaterals of pyramidal cells that are excited monosynaptically by callosal projections (Conti & Manzoni, 1994). This is also a feature characteristic of lateral/surround inhibition. As will become apparent, however, ‘crossed surround inhibition’ is not a unique or anomalous phenomenon. Rather, it is fundamental to bilateral cortical interactions (Tang *et al.* 2007). It is only when viewed in this light that the adaptive utility of inter-hemispheric inhibition is revealed (Cook, 1984).

### Crossed surround inhibition: sensory

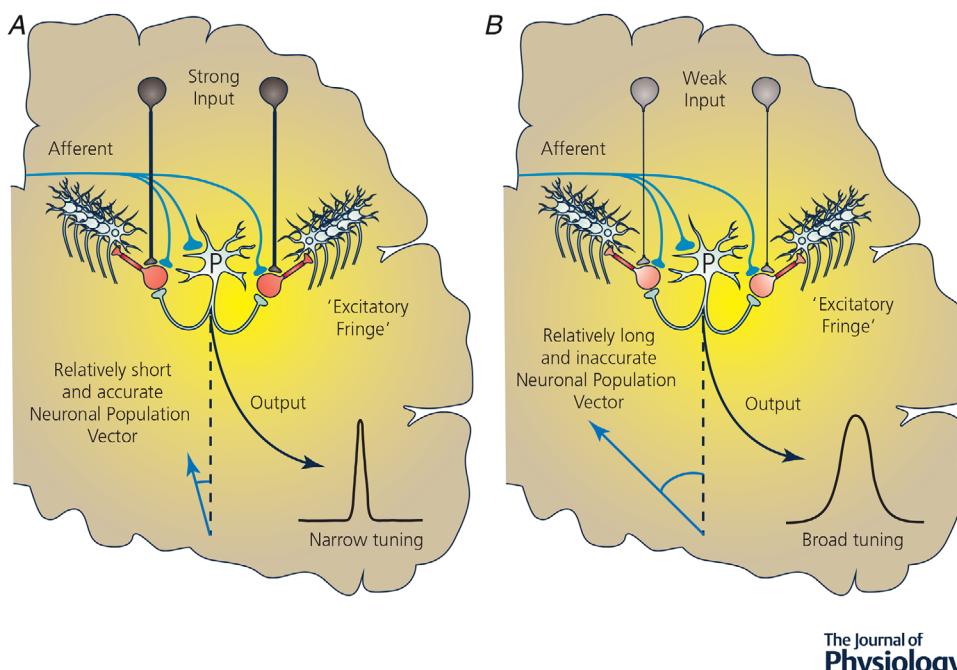
Jones and Powell (1969) proposed that callosally mediated surround-inhibition assumes a role in sensory discrimination that is equivalent in importance to that assumed by ascending sensory pathways. Although relative ‘importance’ is a challenging attribute to gauge, it is nonetheless clear that crossed surround inhibition arising from callosal projections between homotopic regions is a feature of many sensory processing regions in primate and non-primate mammalian brains. A pattern of callosal effect giving rise to a facilitatory centre and a depressing periphery is evident in the visual and auditory cortices of cat (Bianki, 1981). Surround mechanisms mediated by

transcallosal connections have also been demonstrated for several vision-processing areas in various primate species (Allman *et al.* 1985). In model systems, it has been shown that they accentuate orientation tuning, directional selectivity and velocity sensitivity (Simmons & Pearlman, 1983). Beyond the widely appreciated contribution to the generation of receptive fields close to the vertical midline, through point-to-point retinotopic correspondences across the hemispheres (e.g. Rochefort *et al.* 2009; Schmidt, 2016), callosal projections in visual cortex also appear to play further integrative roles. There are indications that neurons in primary visual areas with bi-hemispheric collaterals provide, through temporal coupling of focal excitatory activity induced in their (bilateral) postsynaptic targets, for the grouping of object features on the basis of temporal correlation (Houzel *et al.* 2002).

As for other cortical regions, callosal axons largely have an excitatory influence upon their immediate targets in the opposite somatosensory cortex (Sloper & Powell, 1979), some of which are inhibitory interneurons (Somogyi *et al.* 1983). The surround inhibition thus realized contributes

to the shaping of neuronal receptive fields (RFs) (Clarey *et al.* 1996; Iwamura *et al.* 2001). It also plays an integrative role, promoting bilateral interactions in contexts in which these are functionally relevant – such as in determining the orientation of an obstacle (Shuler *et al.* 2001).

The auditory cortex is of particular interest. Whereas for cortical regions that mediate vision (Newsome & Allman, 1980) and somatosensation (Iwamura *et al.* 2001) callosal fibres largely (but not exclusively) innervate the mid-line zone, inter-hemispheric projections are distributed across the full extent of the auditory cortex (Kitzes & Doherty, 1994; Bamiou *et al.* 2007). In connecting homotopic and heterotopic cortical areas, it is thus redolent of the organization that characterizes the cortical motor network (Ruddy *et al.* 2017). There exist at least two classes of microcircuit in layer 5 of mouse auditory cortex that mediate responses to callosal inputs. Callosal projections onto corticocortical pyramidal neurons induce direct excitation and feedforward inhibition, whereas inputs to corticocollicular pyramidal neurons result in direct excitation (Rock & Apicella, 2015). A particular role in extracting and refining the complex temporal information



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**Figure 4.** Author's representation of the hypothesis that the directional accuracy and speed of upper limb movements are achieved via circuits tuned variably by local inhibitory mechanisms, as described and illustrated in Georgopoulos and Carpenter (2015) and Mahan and Georgopoulos (2013)

Afferent inputs (excitatory) are shown in cyan. The red cells are inhibitory interneurons. The pyramidal cell labelled P is subject to focused excitatory drive. The other pyramidal cells make up the 'excitatory fringe'. It is hypothesized that 'strong input' to inhibitory interneurons (A) sharpens the locus of motoneuron excitation by attenuating the contribution of the excitatory fringe. This results in a reduction of the directional tuning width and the generation of an accurate and short population vector. In contrast, 'weak input' to inhibitory interneurons (B) results in an increase in the directional tuning width and the generation of a less accurate and longer population vector – corresponding to a faster but less accurate movement. The author's original artwork is available at: [https://commons.wikimedia.org/wiki/File:Motor\\_directional\\_tuning\\_hypothesis.jpg](https://commons.wikimedia.org/wiki/File:Motor_directional_tuning_hypothesis.jpg) It was published under a Creative Commons Attribution-Share Alike 4.0 International license.

derived from natural sounds has been ascribed to the coordinated processing by both hemispheres made possible by the feedforward inhibition to which these projections give rise (e.g. Villa *et al.* 2007; Rock & Apicella, 2015). As in other areas of cortex, recurrent collateral axons are also instrumental in mediating the inhibition observed in the immediate vicinity of neurons that receive callosal projections from the homotopic regions of the contralateral hemisphere (Kitzes & Doherty, 1994). A further integrative function has been ascribed to crossed surround inhibition identified in the auditory cortex (e.g. Irvine *et al.* 1996; Blackwell & Geffen, 2017). In bats, for example, neurons in this region are responsive to the combination of the emitted biosonar pulse and its echo, with a specific echo delay. Balancing the delay maps of the two hemispheres in the analysis of orientating echo sounds is accomplished via bilateral interactions that comprise focal facilitation and widespread lateral inhibition (Tang *et al.* 2007).

### Crossed surround inhibition: motor

If, as has been suggested (e.g. Tang *et al.* 2007), bilateral interactions of this nature are among the most fundamental mechanisms of cortical processing, they should also be found in motor systems. In this regard, the findings of Asanuma and Okuda (1962) have been extended on the basis of studies in a number of mammalian species. For example, Chapman *et al.* (1998) reported that in rat, the initial monosynaptic response to callosal input in layer V neurons of M1 is followed by polysynaptic activation of a much larger and more spatially diffuse population of neurons. The inhibitory action of these cells, for example those located within layer II–III, is believed to contribute to the potentiation of a later component of the response generated by monosynaptic input to layer 5, in a fashion that serves to narrow the extent of motor output. The organization described by Chapman *et al.* is thus consistent with the more general conjecture that transcallosal projections onto pyramidal neurons in the deep cortical layers of M1 serve to enhance the excitatory focus of other (e.g. thalamocortical) inputs (Shramm & Kharitonov, 1984).

The explanatory power of the studies conducted by Asanuma and Okuda (1962) is derived from the carefully titrated stimulation of pyramidal tract cells in homotopic regions of the opposite cortex, rather than (as is otherwise frequently the case) direct stimulation of callosal fibres. As Asanuma and Okuda (1962) point out, if a relatively large number of callosal fibres are activated (by whatever means), the focal excitatory effect is masked by the overlapping and summative influence of those fibres that project onto interneurons in the opposite hemisphere that mediate the expression of surround

inhibition. Although they cannot provide the spatial or temporal specificity of the methods employed by Asanuma and Okuda, complementary information can be derived from studies in which intracortical microstimulation is used to assess changes in motor output following (e.g. lidocaine-induced) suppression of the homotopic area in the opposite hemisphere. In this context, the vibrissa motor cortex in rats is employed frequently as a model system. On the basis of a series of studies of this nature (e.g. Maggiolini *et al.* 2007, 2008), it was surmised that stimulated sites in receipt of facilitatory input via the corpus callosum assume a particular role in preserving the size, shape and excitability of vibrissal representations. For those sites subject to an inhibitory influence of the opposite hemisphere, a role in maintaining a boundary between representations of the vibrissa and the forelimbs was reported. The view that the balance between crossed (focal) facilitation and (lateral/surround) inhibition helps maintain the definition of representations within motor cortex is further supported by studies in which preservation of the corpus callosum prevents encroachment by representations of the vibrissae and the hindlimb into areas with projections to muscles innervated via the brachial plexus, which is otherwise observed following total brachial plexus root avulsion (Zhang *et al.* 2015).

### Functions and features of crossed surround inhibition

The contrast enhancing function of surround/lateral inhibition is a motif of transcallosal interactions in the sensory and motor cortices. The principal functional unit of callosal influences, comprising a ‘facilitatory centre and depressing periphery’, serves as a ‘sculptor’s chisel’ (attributed by Bianki (1981) to Ukhtomskii (1966)) that shapes the influence of converging inputs to pyramidal neurons. Critically, the narrowing of the excitatory focus that occurs through this means is reciprocal in nature (Bianki & Makarova, 1980). Increases in surround inhibition in one hemisphere give rise to a reverse (i.e. symmetrical and selective) influence on neurons in the contralateral hemisphere (Bianki & Shrammaprile, 1985). The reciprocal nature of callosal connections is also central to arguments that they perpetuate *intrahemispheric* function, extending onto the contralateral hemisphere intrinsic networks of intracortical short- and/or long-range connections (Schmidt, 2016; see also Bianki, 1981). Thus conceived, the recruitment of contralateral ensembles increases the computational resources available to perform a given task (Ferrandez, 2016). These functions are not, however, exclusive. An architecture that, for example, provides for the sharpening of movement-related neuronal activity through crossed surround inhibition necessarily also

promotes an ‘integrative’ propensity for simultaneous symmetrical movement. Modelling key features of the supporting neural architecture can also delineate the system properties that emerge as a consequence of crossed surround inhibition.

O’Hashi *et al.* (2018) developed a neural mass model of the columnar organization of early visual cortex in which each cortical site is characterized as a local pool of inhibitory interneurons connected mutually to an excitatory pool of (pyramidal) neurons. Cortical sites were connected laterally (both within and across hemispheres) via excitatory projections. Subject to reasonable assumptions that callosal connections are relatively fast (Innocenti *et al.* 1995; Aboitiz, 2017), topographically precise (Innocenti, 1986; Rochefort *et al.* 2007) and have synaptic efficiency roughly equivalent to intra-hemispheric projections, a number of attributes were exhibited by the model. Spontaneous (emerging as under anaesthesia) activity patterns corresponding to maps associated with cardinal and oblique orientations registered experimentally, and orientation state transitions were obtained. In this context, the functional contributions of cortical sites in the two hemispheres were such as to suggest that they were coupled as a single unit. The observation that inter-hemisphere synchrony was equivalent to intra-hemisphere synchrony was taken to further imply that the inter-hemispheric connections are as functionally efficient as intra-hemispheric connections (cf. Jones & Powell, 1969). Notably, the maps corresponding to cardinal and oblique orientations emerged as transient attractor states exhibiting features similar to those ascribed to the pattern dynamics of bimanual coordination. By virtue of extending the computational resources that are available, the distribution of task-related neural activity across the two hemispheres also increases robustness. During motor planning, coupled (via callosal projections) preparatory activity that predicts specific movement directions can be registered in premotor cortex neurons in both hemispheres. If premotor circuits in only one hemisphere are silenced (using optogenetic methods), recovery of task-specific neural activity occurs rapidly, driven by input from the opposite hemisphere. In contrast, bilateral photo-inhibition disrupts preparatory activity. In computational models of this preparation, it is the presence of reciprocal callosal connections in particular that is required to reproduce the stability observed experimentally (Li *et al.* 2016).

The traditional inter-hemispheric competition model relies on the conception that GABAergic interneurons subject local pyramidal neurons to inhibition that is promiscuous and undifferentiated (e.g. Fino & Yuste, 2011; Packer & Yuste, 2011). With respect to the inhibition that is mediated by callosal fibres, however, it is apparent that this is in fact highly differentiated, and reflects the

functional specialization of neurons (Lee *et al.* 2014) and local circuits in the various cortical regions to which these fibres project (Ferrandez, 2016).

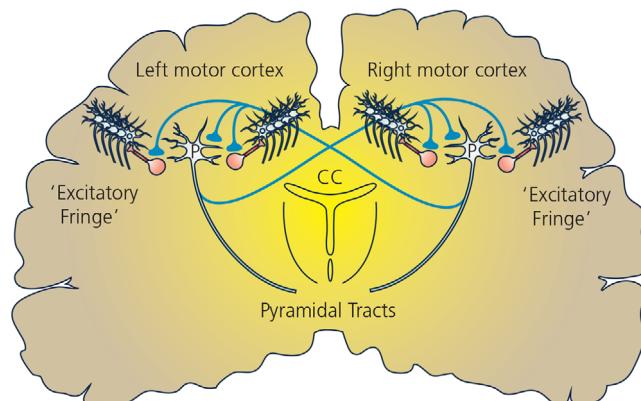
Several forms of differentiation can be discerned. At the most embracing level, each area of cortex projects callosal fibres not only to homotopic regions in the opposite hemisphere, but also to heterotopic regions (Miller & Vogt, 1984; Innocenti, 1986; Chovsepian *et al.* 2017; Ruddy *et al.* 2017). The projection patterns are in most cases reciprocal. Although homotopic and heterotopic projections can arise from distinct cortical layers, in some cases individual neurons bifurcate axons to more than one region of the opposite hemisphere (Innocenti, 1986). With respect to the different laminae in which the projections terminate, the alterations in the balance between excitation and inhibition that are brought about by callosal input can vary markedly. Furthermore, the differences between layers in this respect do not remain constant across cortical regions. For example, in rat somatosensory cortex, GABA<sub>B</sub> receptor-mediated inhibition of layer 5 pyramidal neurons, via transcallosal projections, appears to act upon the apical dendrites via layer 1 interneurons. In this preparation, layer 2/3 pyramidal neurons are not subject to inhibition by callosal input (Palmer *et al.* 2012, 2013). In contrast, recordings from retrosplenial (RSC) cortex in mice suggest that layer 2/3 pyramidal neurons are inhibited profoundly by callosal input acting via parvalbumin (PV)-expressing GABAergic interneurons, whereas thick-tufted but not thin-tufted pyramidal neurons in layer 5 were subject to excitation (Sempere-Ferrández *et al.* 2018).

The distinct response profiles registered for thick-tufted and thin-tufted pyramidal neurons in layer 5 points to further basis for differentiation. Specifically, distinct classes of projection neurons exhibit different changes in the balance between excitation and inhibition brought about by callosal input. The levels of callosally evoked excitation and feedforward inhibition that can be recorded in layer 5 of mouse prelimbic prefrontal cortex are greater in cortico-thalamic neurons than in cortico-cortical neurons. Although in both cases the inhibition is brought about largely by PV-expressing GABAergic interneurons that receive monosynaptic, glutamatergic input from the contralateral hemisphere, the differentiated response profiles are determined, at least in part, by differences in the intrinsic physiology of the cortico-cortical and cortico-thalamic neurons (Anastasiades *et al.* 2018; see also Lee *et al.* 2014). By way of contrast, in (mice) auditory cortex, a similar pattern of variation between the response profiles of layer 5 cortico-cortical and cortico-collicular neurons, appears to be due to a preferential (feed-forward) activation of cortico-cortical pyramidal neurons by PV-expressing inhibitory interneurons. In the absence of strong suppression by inhibitory interneurons, the cortico-collicular projecting neurons exhibit greater

facilitation in response to callosal input (Rock & Apicella, 2015). In this case, therefore, the variations in the response profiles of the two types of pyramidal neuron are brought about by differences in the architecture of the networks in which they are embedded, rather than being attributable to a distinction in their intrinsic physiology.

In mouse the RSC forms part of a subnetwork that mediates the transduction of information between sensory areas and higher-order association areas (Zingg *et al.* 2014). Callosal fibres excite monosynaptically layer 6 pyramidal neurons in the agranular subdivision of the RSC. In addition, PV-expressing GABAergic interneurons, in this deep cortical layer, receive synapses on dendrites and somata and are activated directly by the contralateral hemisphere via callosal projections (Karayannidis *et al.* 2007). The direct (feedforward) callosal activation of GABAergic interneurons observed in this case (similar to that shown in Fig. 5) can be differentiated from an organization whereby IPSPs are driven by axon collaterals (Fig. 6) of the pyramidal cells excited monosynaptically by callosal projections (Conti & Manzoni, 1994). In the period since the first demonstrations of recurrent collateral inhibition in pyramidal tract neurons (e.g.

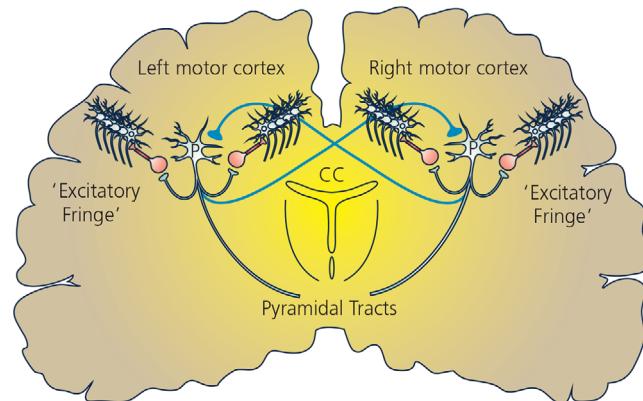
Phillips, 1959; Stefanis & Jasper, 1964b; Kameda *et al.* 1969), it has been proposed that these recurrent collaterals, and the intercalated interneurons onto which they project, provide the substrate for the bell-shaped directional tuning curve that characterizes the discharge of pyramidal cells in motor cortex (Georgopoulos & Stefanis, 2007). Indeed, a substantial proportion of individual (presumed GABAergic inhibitory) interneurons within primate M1 can be classified on the basis of their directional tuning (Merchant *et al.* 2008). In principle, while reductions of discharge time and constriction of excitatory extent induced by collateral inhibition provide for both temporal and spatial enhancement of motor output (Kameda *et al.* 1969; Isomura *et al.* 2009), it has also been argued that feedback inhibition and feedforward inhibition assume complementary computational roles (Chen *et al.* 1995). In this scheme, feedforward inhibition sharpens the focus of motor cortical activation to a greater degree, whereas feedback inhibition increases the temporal precision of motor output. With respect to callosal input more particularly, the temporal dynamics of the inhibition that it brings about are also determined by receptor subtype. In the context of direct (feedforward) inhibition,



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**Figure 5.** A schematic representation of the manner in which the contrast-enhancing and integrative functions of crossed surround inhibition may be instantiated via direct callosal activation of GABAergic interneurons

Pyramidal tract cells are shown in black. The pyramidal cells labelled P are subject to focused excitatory drive. The red cells are inhibitory interneurons. Callosal projections (excitatory) are shown in cyan. The inhibitory influence upon pyramidal tract cells in the surround region of the opposite hemisphere ('excitatory fringe') in this case arises from local feed-forward inhibitory circuits. A key assumption is that the inter-hemispheric interactions arising from this configuration can be reciprocal (e.g. Bianchi & Makarova, 1980; O'Hashi *et al.* 2018). The author's original artwork is available at: [https://commons.wikimedia.org/wiki/File:Crossed\\_surround\\_inhibition\\_feedforward.jpg](https://commons.wikimedia.org/wiki/File:Crossed_surround_inhibition_feedforward.jpg) It was published under a Creative Commons Attribution-Share Alike 4.0 International license.



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**Figure 6.** A schematic representation of the manner in which the contrast-enhancing and integrative functions of crossed surround inhibition may be instantiated via axon collaterals of the pyramidal cells excited monosynaptically by callosal projections

Pyramidal tract cells are shown in black. The pyramidal cells labelled P are subject to focused excitatory drive. The red cells are inhibitory interneurons. Callosal projections (excitatory) are shown in cyan. The inhibitory influence upon pyramidal tract cells in the surround region of the opposite hemisphere ('excitatory fringe') in this case arises from local recurrent inhibitory circuits. A key assumption is that the inter-hemispheric interactions arising from this configuration can be reciprocal (e.g. Bianchi & Makarova, 1980; O'Hashi *et al.* 2018). The author's original artwork is available at: [https://commons.wikimedia.org/wiki/File:Crossed\\_surround\\_inhibition\\_recurrent.jpg](https://commons.wikimedia.org/wiki/File:Crossed_surround_inhibition_recurrent.jpg) It was published under a Creative Commons Attribution-Share Alike 4.0 International license.

the IPSPs generated in inhibitory interneurons following transcallosal monosynaptic EPSPs have a component that depends on GABA<sub>A</sub> receptors, and another that is contingent upon GABA<sub>B</sub> receptors (Conti & Manzoni, 1994; see also Chowdhury & Matsunami, 2002).

In summary, and consistent with the general observation that callosal projection neurons are extraordinarily diverse (Fame *et al.* 2011), the local inhibition that these neurons may promote is differentiated in many ways. This variegation arises not only from cytoarchitectural features, such as the brain regions and cortical layers in which the cell bodies of callosal projection neurons are located, it is also attributable to the intrinsic morphology and physiology of the target cells onto which they project, and the configuration of the networks in which these targets are embedded. While the patterns of inhibition elicited by callosal projections are in part an emergent property of these local networks, the actuating excitatory drive is necessarily also selective and highly differentiated (Carson, 2005). In short, the recruitment profile of inhibitory interneurons engaged (directly or indirectly) by callosal input is extremely complex, and belies any model in which the function of inter-hemispheric inhibition is represented as simply modulating the overall excitability of brain networks. As Cook (1984) perceived more than 35 years ago, the existence of inter-hemispheric inhibition does not suggest that unilateral activity generates contralateral ‘deactivation’, or that it brings about asymmetries of excitation between the cerebral hemispheres. Rather, acting through the mechanism of crossed surround inhibition, it provides the basis for ‘complementary patterns of neuronal firing’ (p. 121).

### Limitations of IHI for investigating inter-hemispheric inhibition in humans

In a fitting observation, Uttal (2016) notes that, ‘our theories are, to a much greater degree than we appreciate, creatures of whatever technology is available at any stage of history’ (p. xii). In this vein, it will be argued that the inter-hemispheric competition model has been sustained, and clinical interventions based on the notion of an ‘inter-hemispheric imbalance’ promoted, by a misplaced dependence upon experimental methods that depend upon TMS. More specifically, erroneous assumptions have been made concerning that which can be revealed by the IHI technique.

As emphasized previously, IHI is an electrophysiological phenomenon whereby the magnitude of a ‘test’ motor evoked potential (MEP), obtained in response to stimulation delivered over M1, is decreased by the application of a prior ‘conditioning’ stimulus (CS) to the opposite M1 (Ferbert *et al.* 1992). The intensity of the CS

employed to elicit IHI is in almost all instances well above that required to generate a MEP in quiescent muscles of the opposite limb. For example, Ferbert *et al.* (1992) used a CS that was 20% above the motor threshold. When varied systematically in relation to the active motor threshold, it becomes apparent that (short and long latency) IHI can be invoked only when the CS intensity is well above (e.g. >1.2 active motor threshold) the level at which descending corticospinal volleys are generated (see Fig. 6 in Ni *et al.* 2008).

A principal limitation arising from the use of TMS in this context is that it has extremely poor spatial definition. When modelled on the basis of MEPs generated by direct electrical stimulation of the exposed cortex in individuals undergoing neurosurgery, TMS delivered at 120% of resting motor threshold exerts a stimulating effect that can extend over one or two neighboring gyri, and span an area of several cm<sup>2</sup> (Opitz *et al.* 2014). To put this in context, estimates of the number of neurons within a unit volume below 1 mm<sup>2</sup> at the surface of the primary motor cortex in chimpanzee are in the region of 55,000 (Young *et al.* 2013). It is clear therefore that millions of neurons are likely to be affected directly by TMS. Since cortico-cortical callosal projections terminate both in homotopic sub-regions of the opposite hemisphere (Innocenti *et al.* 2017) and also in heterotopic regions (Innocenti, 1986; Chovsepian *et al.* 2017), there is no reason to suppose that in the IHI paradigm, the transcallosal effect of the CS will be any more closely circumscribed. Indeed, it has long been appreciated that even when direct electrical stimulation is applied (for example Opitz *et al.* (2014) induced a stimulation area of a few mm<sup>2</sup> using currents below 20 mA in humans), the spatial extent of the callosal stimulating effect is very much greater than under natural conditions (Doty & Negrao, 1973). It is also clear that both magnetic and electrical stimulation of M1 induce high-frequency (~600 Hz) repetitive discharge in pyramidal neurons, which is quite distinct from normal physiological discharge frequencies of 100 impulses/s (Lemon & Kraskov, 2019). As a consequence, even a single discrete (artificial) stimulus can invoke trans-synaptic responses in the majority of neighbouring neurons (Maier *et al.* 2013). A key observation in this regard is that, while relatively weak electrical stimuli have an excitatory effect, as the effective intensity of the stimulation is increased, inhibition that affects ‘an astonishingly large number of neurons’ can be generated (Krnjević *et al.* 1966). This is a characteristic of both intracortical and transcallosal stimulation (Asanuma & Okamoto, 1959; Krnjević *et al.* 1966).

The practical consequences of these factors in relation to IHI have been recognized for some time (Hanajima *et al.* 2001; Bäumer *et al.* 2006; Ferbert *et al.*, 1992). In short, the poor spatial definition of the transcallosal volley brought about by the conditioning magnetic stimulus,

and the intense trans-synaptic bombardment of neurons to which TMS gives rise both promote the massed and undifferentiated invocation of inhibitory processes that in normal physiological conditions are precisely engaged and serve to narrow the excitatory focus of M1 activation. Paradoxically, therefore, in applying the IHI technique, the defining and integrating inter-hemispheric interactions that occur through crossed surround inhibition are masked by the artificial means through which the supporting neural networks are interrogated. As a consequence of the disproportionate significance ascribed to results obtained using the IHI method, the adaptive functions of inter-hemispheric inhibition may have been largely misconceived.

## Additional clinical evidence

It is a central tenet of the inter-hemispheric competition model that the contralesional hemisphere brings about inhibition of the ipsilesional hemisphere via callosal pathways that link the two sides of the brain. In this scheme, it follows that callosal integrity (i.e. reflecting the quality of the medium through which inter-hemispheric interactions occur) **should be positively related to the extent of inhibition, and thus to the magnitude of the motor deficits that are exhibited following stroke**. In other words, better callosal connectivity should, in the terms of this model, provide greater scope for inhibition of the ipsilesional hemisphere by the contralesional hemisphere. If in contrast, inter-hemispheric projections serve primarily to focus and integrate neural activity in the opposite side of the brain via mechanisms such as surround inhibition, callosal integrity in stroke survivors should be positively related to motor capability. That is, greater, or improved, callosal connectivity should entail better motor capability. There is a steadily accumulating body of empirical evidence, derived largely from neuro-imaging studies, that provides a basis upon which to assess these contrasting predictions. Due to the diversity of the imaging methodologies and analysis techniques that have been applied, meta-analyses are not yet available. It is, however, possible to **provide a narrative summary of the key findings**. These are consistent in indicating that the structural integrity of transcallosal pathways is positively associated with motor capability following stroke.

The magnetic resonance imaging variant referred to as diffusion weighted imaging (DWI) is capable of providing **quantifiable detail concerning the microstructural organization of white matter**, and in some implementations it permits the course of individual white matter tracts to be resolved. The diffusion tensor model, first described by Basser *et al.* (1994), is the mathematical framework that has been used most widely to make inferences that relate diffusion-weighted images

to the local tissue microstructure. The model is, however, inadequate for regions that contain complex architectures such as crossing fibres (Alexander *et al.* 2002; Tuch *et al.* 2002; Jeurissen *et al.* 2013) – a limitation that extends to the lateral cortical projections of the corpus callosum (Jeurissen *et al.* 2011). As many of the transcallosal projections that connect nodes of the cortical motor network cannot, therefore, be detected using the diffusion tensor model (Meng & Zhang, 2014; Ruddy *et al.* 2017), the present summary is restricted to studies that have used non-tensor diffusion models, such as constrained spherical deconvolution (CSD) imaging and diffusion spectrum imaging (DSI).

Assessing the fractional anisotropy (FA) – higher values of which are obtained for brain regions that are heavily myelinated or that have densely packed axons – of tracts defined within the midsagittal corpus callosum using the CSD method, Auriat *et al.* (2015) reported a negative association between FA values and completion times for the Wolf motor function test (WMFT), in 27 chronic stroke survivors who ranged widely in the degree of arm impairment that was exhibited (Fugl–Meyer upper limb score (FM-UL) 7–63). In a more severely impaired (FM-UL  $\leq$  30/66) group, Hayward *et al.* (2017) observed that CSD-derived FA values for callosal streamlines defined between prefrontal, premotor and primary motor regions were in all cases positively associated with FM-UL score. It does, however, appear that for chronic stroke survivors, the negative associations of FA values with motor function (e.g. WMFT completion time), and the positive associations with the FM-UL score, are more robust for callosal streamlines linking prefrontal regions and premotor/supplementary motor area regions than for those defined for primary motor regions (Mang *et al.* 2015; Hayward *et al.* 2017). The FA values derived for callosal fibres projecting between primary sensory, and parietal, temporal and visual areas seem to have minimal predictive power in relation to measures of either motor function or impairment (Mang *et al.* 2015). Using DSI tractography, Koh *et al.* (2018) observed that in a group of chronic stroke survivors with lesions impinging on callosal motor fibres, there was a positive association between FM-UL score and the generalized fractional anisotropy measure derived for streamlines passing between homologous regions of the cortical motor network.

Although changes in the diffusion characteristics of white matter bundles are substantially less marked than those observed for cortical grey matter in the days immediately following middle cerebral artery occlusion (Zhang *et al.* 2018), decreases in the microstructural integrity of callosal fibres distal to the focal lesion (i.e. Wallerian degeneration) are evident within 6 months following middle cerebral artery and (subcortical) pyramidal tract infarcts (Gupta *et al.* 2006; Radlinska *et al.* 2012; see also Li *et al.* 2015, 2016). Measurements

of structural connectivity obtained in the subacute phase following stroke, therefore, provide the best possible basis upon which to resolve the presence of associations between the structural integrity of transcallosal pathways and motor capability following stroke. This is particularly the case if the observations are made within the time frame during which Wallerian degeneration of callosal fibres is unlikely to have occurred to a significant degree. It might be remarked that assessments of variations in functional connectivity (for example derived using resting state functional magnetic resonance imaging) are of limited utility in this regard, as these measures are necessarily sensitive to the immediate changes in the dynamic properties of neural circuits within the ipsilesional hemisphere that occur as a direct consequence of stroke. It is, however, feasible to evaluate whether, during the subacute phase, motor capability is positively related to the structural connectivity of transcallosal projections.

In a group of patients for whom the DWI was typically undertaken within the first 10 days following stroke, probabilistic tractography-derived indices of the white matter tract volumes defined between regions of interest encompassing left and right M1 were predictive of motor outcomes (box and block test) assessed 3 and 6 months later (Lindow *et al.* 2016). Employing DSI tractography, Granziera *et al.* (2012) noted that generalized fractional anisotropy values of white matter streamlines passing through left and right supplementary motor area, registered within 1 week following stroke, predicted scores on the motor part of the NIH Stroke Scale (NIHSS) obtained 6 months later. Using DWI sequences with an angular resolution lower than that required for the use of methods such as CSD, Li and colleagues performed probabilistic tracking of streamlines seeded in left and right M1, and reported a positive association between FA values and Fugl–Meyer scores for individuals having sustained subcortical ischaemic lesions 21–135 (median 32) days previously (Li *et al.* 2016, see also Li *et al.* 2015).

In short, in stroke survivors, the structural integrity of callosal fibre bundles that connect nodes of the cortical motor network is positively related to motor capability. The association is expressed both when assessed soon (< 10 days) after the brain insult and many months later. This pattern of outcomes is consistent with the proposition that the callosal projection neurons contained within these fibre bundles support the focusing and integration of neural activity in the opposite side of the brain. An explanation is thus also provided for the bilateral deficits in motor control that occur following unilateral brain injury (e.g. Desrosiers *et al.* 1996).

The emphasis in this section has been upon the manifestation of associations that are inconsistent with one particular (functional) model, inter-hemispheric competition, but consistent with an alternative model, in

which the two hemispheres act cooperatively to sculpt the output of neural circuits. Although the alternative model arises from a specific hypothesis concerning the physiology of callosally mediated inhibition, in interpreting associations between callosal integrity and motor deficits exhibited following stroke, the level of analysis is necessarily functional. That is, the inference drawn given the presence of these relationships does not in itself corroborate the existence of any specific form of callosally mediated inhibition.

## Summary and conclusions

The practical and explanatory limitations of the ‘inter-hemispheric competition’ model, for example, as it has been applied to stroke, arise from a fundamental misunderstanding of the physiological properties exhibited by inter-hemispheric (callosal) projections in mammalian brains. These projections do not give rise to promiscuous and undifferentiated inhibition, or bring about asymmetries in excitation between the cerebral hemispheres. Rather, they perform contrast enhancing and integrative roles via mechanisms such as surround/lateral inhibition that shape the influence of converging inputs to pyramidal neurons. The narrowing of excitatory focus promoted by inter-hemispheric inhibition is a functional motif that is strongly conserved across mammalian sensory and motor cortices. It is a highly differentiated process that reflects the functional specialization of neurons and local circuits in the various cortical regions to which callosal fibres project. Any attempts to manipulate inter-hemispheric inhibition for therapeutic gain must, in order to be successful, respect its cardinal properties.

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