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Targeting interhemispheric inhibition with neuromodulation to enhance stroke rehabilitation

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ABSTRACT

Background/Objectives: Interhemispheric inhibition in the brain plays a dynamic role in the production of voluntary unimanual actions. In stroke, the interhemispheric imbalance model predicts the presence of asymmetry in interhemispheric inhibition, with excessive inhibition from the contralesional hemisphere limiting maximal recovery. Stimulation methods to reduce this asymmetry in the brain may be promising as a stroke therapy, however determining how to best measure and modulate interhemispheric inhibition and who is likely to benefit, remain important questions.

Methods: This review addresses current understanding of interhemispheric inhibition in the healthy and stroke lesioned brain. We present a review of studies that have measured interhemispheric inhibition using different paradigms in the clinic, as well as results from recent animal studies investigating stimulation methods to target abnormal inhibition after stroke.

Main findings/Discussion: The degree to which asymmetric interhemispheric inhibition impacts on stroke recovery is controversial, and we consider sources of variation between studies which may contribute to this debate. We suggest that interhemispheric inhibition is not static following stroke in terms of the movement phase in which it is aberrantly engaged. Instead it may be dynamically increased onto perilesional areas during early movement, thus impairing motor initiation. Hence, its effect on stroke recovery may differ between studies depending on the technique and movement phase of eliciting the measurement. Finally, we propose how modulating excitability in the brain through more specific targeting of neural elements underlying interhemispheric inhibition via stimulation type, location and intensity may raise the ceiling of recovery following stroke and enhance functional return.

1. Introduction

Stroke is a leading cause of death and disability in the developed world. Unfortunately many who survive stroke never achieve complete restoration of function. Extensive physical therapy is the current best practice to maximise return of function after stroke, however, within several months many stroke survivors reach a plateau in the gains made with rehabilitation alone, leaving some degree of residual disability affecting activities of daily life [1]. Non-invasive neuromodulation techniques such as repetitive transcranial magnetic stimulation (rTMS) have been extensively trialled to determine their effectiveness at augmenting motor recovery after stroke. Although individual gains have been reported [2–7], there is no convincing evidence of benefit over and above the ceiling of recovery that is reached after approximately six months of usual rehabilitation [1,8,9]. It is clear that new approaches are required to enhance the effects of physical therapy and elevate the ceiling of recovery, to reduce the burden of stroke on individuals and their families.

Unilateral stroke is classically regarded as leading to impaired inhibition between the cerebral hemispheres. The interhemispheric imbalance model (see Fig. 1) assumes that in the healthy brain inhibition is balanced between the hemispheres, but predicts that after a stroke there is reduced inhibition from the stroke-affected area onto the unaffected (contralesional) hemisphere. This results in increased excitability of the contralesional

Abbreviations: TMS, Transcranial magnetic stimulation; rTMS, repetitive transcranial magnetic stimulation; GABA, γ-amino butyric acid; tDCS, transcranial direct current stimulation; TBS, theta-burst stimulation; iTBS, intermittent theta-burst stimulation; cTBS, continuous theta-burst stimulation; S-IHI, Short latency interhemispheric inhibition; L-IHI, Long latency interhemispheric inhibition; iSP, ipsilateral silent period; fMRI, functional magnetic resonance imaging.

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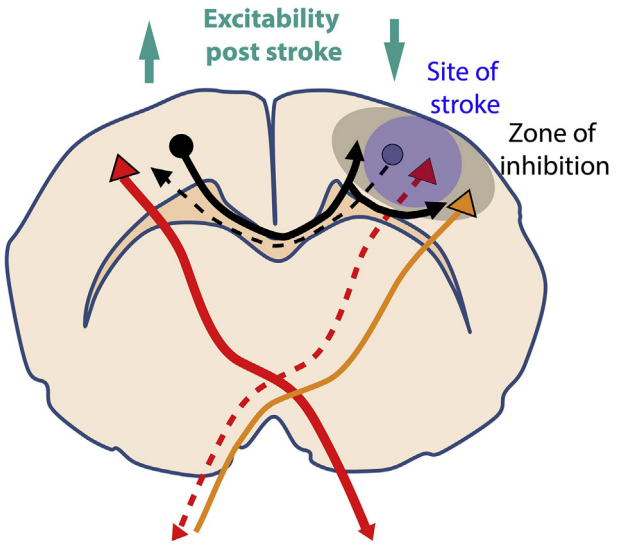

Fig. 1. The interhemispheric imbalance model, which predicts dysfunction after unilateral stroke, as represented by a diagram of the rat brain with unilateral cortical stroke. The interhemispheric imbalance model predicts that each side of the brain inhibits the other equally. After a stroke, the inhibition coming from the stroke-affected hemisphere is decreased (interhemispheric dashed line) alongside a decreased excitability in the peri-lesional tissue. The unaffected hemisphere therefore becomes more excitable and exerts a stronger inhibition onto the peri-lesional tissue. Modulating this zone of inhibition in the peri-infarct tissue appears to be a potential target for stroke therapy.

hemisphere which ultimately leads to excessive interhemispheric inhibition onto ipsilesional cortical areas [10–12]. The connectivity in the residual surviving tissue could conceivably be remapped to recover lost function [13–17], however this excessive imbalanced inhibition is thought to impede neuroplasticity in these areas and limit the gains in motor recovery that can be achieved through rehabilitation [10,18,19]. Recently however, conflicting conclusions have been reported across studies as to whether a true 'imbalance' in interhemispheric inhibition exists in the human brain after stroke [10,20–22]. In the sections that follow, we aim to synthesise current understanding of interhemispheric inhibition after stroke and to assess the validity of current neurostimulation methods for targeting and modulating imbalanced interhemispheric inhibition. We conclude with a consideration of novel neuromodulation techniques and suggest how these alternative methods of neuromodulation may be effective in improving stroke recovery.

2. Interhemispheric inhibition in the healthy motor cortex

Interhemispheric inhibition in the motor cortex is the mechanism by which each hemisphere inhibits the other during the production of voluntary unimanual movements. It is thought that interhemispheric inhibition underlies the rapid inhibition of the contralateral motor cortex that is present during movement initiation, in order to suppress a 'mirrored' movement that may be deleterious to task performance [23–25]. This is mediated via the largest fibre bundle tract in the brain, the corpus callosum [26,27]. Evidence in humans that a transcallosal pathway conveys interhemispheric inhibitory signals despite the predominance of direct excitatory connections between motor areas [23,28–30] was first demonstrated in 1992 by Ferbert et al. The authors pioneered the use of a double transcranial magnetic stimulation (TMS) pulse paradigm using a separate coil positioned over each motor cortex. They reported that stimulating the motor cortex in one hemisphere inhibited movement-related activity initiated by the opposite motor cortex. A suprathreshold 'test' pulse was applied to one hemisphere to elicit a motor-evoked potential, however a 'conditioning' pulse applied to the opposite hemisphere at specific intervals prior to the test pulse reduced the amplitude of the test motor-evoked potential. Since then, two distinct phases of interhemispheric inhibition elicited by the double coil method have been described, the first where conditioning to test pulse intervals are short (6–15 ms; S-IHI), and the second where the conditioning to test interval is long (40–50 ms; L-IHI) [31–34], likely representing the engagement of different neuronal mechanisms in the target motor cortex.

A single TMS pulse applied to the motor cortex can also inhibit tonic ipsilateral muscle activity elicited by sustained muscle contraction [35]. This period of inhibition is lacking in patients with agenesis of the corpus callosum [26] indicating that its origin is transcallosal in nature. Many studies have since utilised this period of inhibition as an alternative measure of interhemispheric communication, calling it the ipsilateral silent period (iSP). There is convincing evidence to suggest that interhemispheric inhibition elicited by the double TMS coil and iSP methods activate different neuronal circuitry under particular circumstances [33]. Firstly, L-IHI and iSP are thought to be mediated by $GABA_B$ receptors [31,36], whereas S-IHI is not influenced by $GABA_B$ receptor activation and may instead rely on $GABA_A$ receptors [31]. Muscle activation also modifies the measurement of S-IHI, however has little effect on L-IHI or iSP [25,33]. Furthermore, interhemispheric inhibition elicited by double TMS coil or iSP methods differentially modulates intracortical circuitry [37,38]. Altogether these studies suggest that iSP and short and long latency IHI should be considered as complementary, not equivalent measures of interhemispheric communication [33]. Since iSP measurements require continuous muscle contraction, this measure provides information related to ongoing cortical motor output during sustained isometric activation, in the absence of visible movement [39]. In contrast, interhemispheric inhibition, as measured using the double TMS coil paradigm, appears more related to the *initiation* of voluntary movement, since it is normally released during movement execution [10]. Since the purpose of interhemispheric inhibition is thought to be preventing unwanted bimanual movements, the double TMS coil method would therefore appear to be more suitable for interrogating the mechanisms relevant to movement initiation. The experimental ease of conducting the iSP measurement however means this method currently dominates the literature. Keeping in mind the differences in the underlying circuitry, we suggest that future studies should compare both measures before making broad claims regarding the influence that interhemispheric inhibition has on either the healthy or stroke-affected brain.

3. Modulation and mechanism of interhemispheric inhibition in the healthy brain

In the healthy brain, interhemispheric inhibition can be modulated using common rTMS paradigms. Short-latency interhemispheric inhibition can be directly modulated by the application of low and high frequency rTMS [40–42], quadripulse TMS [43], theta-burst stimulation (TBS) [44], or bilateral transcranial direct current stimulation (tDCS) via external electrodes [45,46]. Similarly, rTMS applied to one hemisphere has also been shown to alter cortical excitability in the unstimulated hemisphere [47–50], presumably through modulation of interhemispheric communication however the underlying mechanisms remain unknown. In order to investigate the cellular mechanisms underlying interhemispheric inhibition and its modulation by TBS, Barry et al. (2014) recently developed an *in vivo* animal model in healthy adult rats using sharp

electrode intracellular recording [51]. By recording monosynaptic potentials from inside individual pyramidal neurons in response to electrical stimulation of the ipsilateral cerebral cortex, they found that interhemispheric inhibition can be induced in the motor cortical circuitry by focal electrical stimulation of the contralateral motor cortex (see Fig. 2A). The protocols for eliciting interhemispheric inhibition were applied with the limb muscles at rest, and were modelled on those used in human double coil TMS studies [10,35,52,53]. Importantly, interhemispheric inhibition was only observed when the intensity of the conditioning electrical stimulation was set below the threshold to elicit an excitatory post-synaptic potential within the recorded neuron. Thus very low-intensity contralateral electrical stimulation seemed to preferentially target a low-threshold neural circuit which may underlie interhemispheric inhibition. Further work is required to identify the neural elements activated at low threshold by this stimulation, and to determine whether the inhibition is mono- or disynaptic. Interestingly, in the auditory system, there is evidence in other mammals of inhibition between homologous cortical areas, at latencies consistent with a direct transcallosal inhibitory circuit [54].

4. Interhemispheric inhibition in the stroke-affected brain

The disruption of blood flow during a stroke prevents cells in the ischaemic area from being able to maintain ionic gradients across cell membranes and consequently leads to excitotoxic cell death. The resulting region of cell death is surrounded by the peri-infarct or penumbral tissue which displays heightened plasticity following stroke, thought to be related to remapping lost functions into the surviving tissue [55–60]. Remote electrophysiological changes in ipsilesional and contralesional hemispheres are also common [12,26,61–64] and targeting these may be beneficial at enhancing recovery after stroke.

Studies using animal models have identified that over the first week following stroke or cortical injury, excitability in the ipsilesional hemisphere is reduced [62] and the contralesional hemisphere becomes hyper-excitable [61]. Rapid increases in contralesional excitability (within an hour following stroke onset) [65] may represent a release of interhemispheric inhibition as a result of acute damage to callosal circuitry [30]. Over time, with or without intervention, excitability in the contralesional hemisphere normalises, which appears to track with improvements in recovery [66,67]. In human stroke patients, similar changes occur where increased intracortical excitability is observed in the contralesional hemisphere in both the acute [12,68] and subacute [69,70] phases after stroke. Increased contralesional excitability has also been associated with a reduction of inhibition emanating from the stroke-affected tissue [64]. Furthermore patients with severe impairment also retain abnormal contralesional activation [71], whereas those that show substantial recovery over time show a normalisation of brain activity to activation predominantly in the ipsilesional hemisphere [72–76]. This suggests that up-regulating the ipsilesional hemisphere or down-regulating the contralesional hemisphere may be beneficial after stroke [77,78].

Evidence suggesting that stroke can also directly alter interhemispheric inhibition was first presented by Boroojerdi et al. (1996) and later supported by Shimizu et al. (2002). Reductions in interhemispheric inhibition characterized by both the double coil TMS and iSP methods were noted in stroke patients with mixed cortical-subcortical lesions but not in those with purely subcortical lesions, further suggesting that interhemispheric inhibition is predominantly mediated by circuits in the cortex [69,79].

Since the functional role of interhemispheric inhibition in the healthy brain is likely to be associated with the initiation and performance of voluntary movement, Murase et al. [10], hypothesised that meaningful abnormalities in interhemispheric inhibition after stroke would be better detected when active movements of a paretic limb were performed. Indeed in stroke patients, an abnormally strong inhibitory drive from contralesional to ipsilesional hemisphere was seen close to presentation of the go signal to

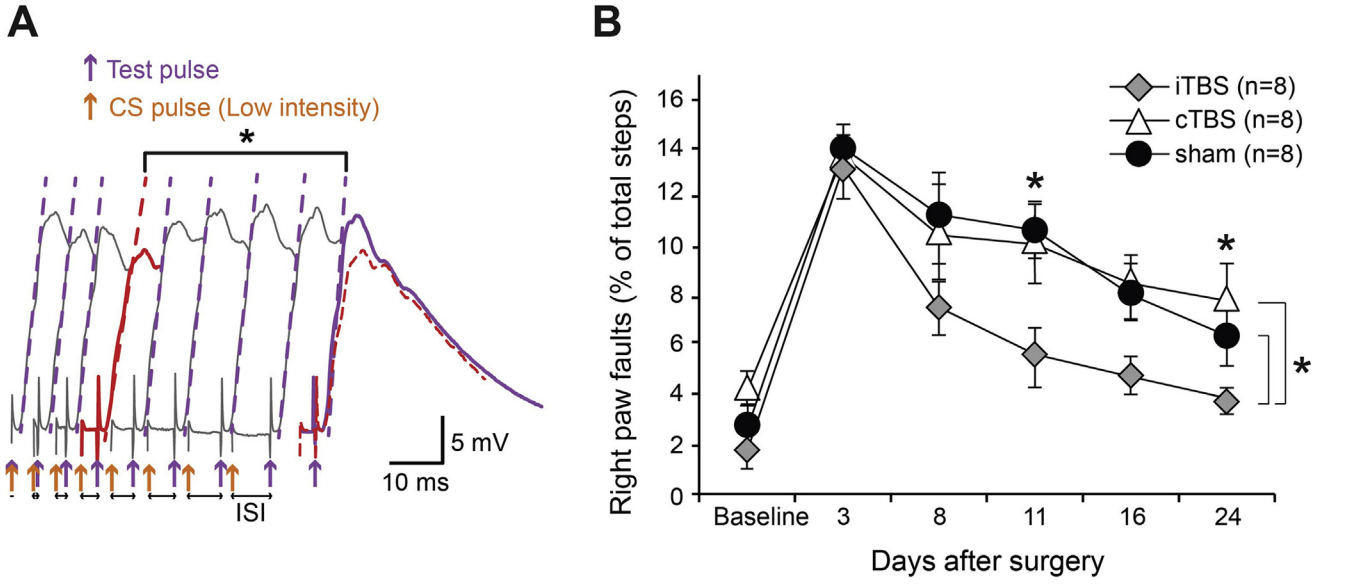

Fig. 2. **(A)** Rodent model of interhemispheric inhibition. Electrical test pulses elicit post-synaptic potentials (shown) recorded *in vivo* in the motor cortex of a rat. When an electrical conditioning stimulus (CS; orange arrows) in the opposite motor cortex, precedes an electrical test pulse (purple arrows) applied in the recorded motor cortex, at specific inter-stimulus intervals (ISI), interhemispheric inhibition is seen as a reduction in the amplitude, and maximal slope of the post-synaptic potential (seen in red). In Barry et al. (2014) this interhemispheric inhibition was abolished in healthy rats by the application of low intensity electrical iTBS to the same conditioning electrode. **(B)** Electrical iTBS applied to the unaffected hemisphere after stroke enhances stroke recovery in rats. Rats with focal lesions in the primary motor cortex received either sham stimulation or electrical iTBS or cTBS over a number of days after stroke. Application of iTBS enhanced recovery on a grid-walking task compared to both cTBS or sham stimulation, suggesting that this may be through modulation of interhemispheric inhibition. Figures reprinted from Experimental Neurology, Barry et al. (2014), Vol 261, 258–266; with permission from Elsevier. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

commence voluntary movement in their paretic hand, suggesting that abnormal interhemispheric inhibition was present during movement preparation. A greater imbalance of interhemispheric inhibition between contralesional and ipsilesional hemispheres, also correlated with poorer performance [10,21], thus it has been proposed that increased inhibition in the ipsilesional hemisphere may limit maximal functional recovery after stroke and contribute to residual motor disability [10,21]. These findings have been fundamental in shaping the interhemispheric imbalance model and many neuromodulatory therapies have been based on this premise of an asymmetric interhemispheric inhibition [80].

Evidence in favor of the interhemispheric imbalance model is apparent in two rare case studies where the symptoms associated with a single hemisphere stroke were alleviated by a second stroke that occurred in the opposite hemisphere [18,19]. Vuilleumier et al. 1996 described a patient initially presenting with a right-sided parietal infarct resulting in severe unilateral neglect. Notably the symptoms of neglect abruptly disappeared after the patient experienced a second stroke in the left frontal lobe. More recently, Sauerbrei & Liepert (2012) reported a similar case of a patient initially presenting with severe right-sided hemiparesis after a left-hemisphere haemorrhage. Remarkably the hemiparesis disappeared almost completely after a later right-parietal infarct. In both of these reported cases, the investigators state that the rapid time course of recovery seen in their patients cannot entirely be explained by the brain's natural ability to spontaneously recover, and they speculate that rebalancing of interhemispheric rivalry played a key role in their patients' recovery. Of note there have also been reports of worsening function after a second contralesional stroke [13,15,16]. However, all were due to subcortical infarcts, which are less likely to affect interhemispheric inhibition than a subsequent cortical infarct [69,79].

The presence of altered interhemispheric inhibition after stroke is not universally agreed, with different groups reporting variable results. In some studies, no asymmetry in interhemispheric inhibition from the unaffected hemisphere was detected [20,81,82]. Others have demonstrated: a greater inhibition from the ipsilesional onto contralesional hemispheres [83], that the contralesional hemisphere does not over-inhibit the ipsilesional hemisphere [84], and that reducing contralesional inhibition results in poorer performance [85], indeed all opposing the interhemispheric inhibition model. A common factor linking all of these studies is that the measurement of interhemispheric inhibition using the double TMS coil method or iSP was performed at rest or during sustained isometric contraction, respectively.

Functional connectivity and dynamic causal modelling analyses of fMRI data suggest that there are striking differences in interhemispheric connectivity during active movements of the paretic limb compared with the limb at rest [78,86,87]. During active movements in stroke patients (typically repetitive fist closures), there is a stronger inhibitory influence of the contralesional motor cortex onto the ipsilesional motor cortex [78,86] and a disinhibition of the contralesional hemisphere from the ipsilesional hemisphere [87]. This disruption to functional connectivity originating contralesionally also predicts poorer motor performance [78,86,88,89]. In comparison, in stroke patients at rest there is normal connectivity between motor areas compared with healthy controls [86]. These findings collectively suggest that interhemispheric inhibition is dynamically influenced by movement and is likely to be more prominent and aberrantly engaged in the peri-lesional areas during the critical movement preparation and early execution periods as opposed to when the affected limb is completely at rest or isometrically contracted. To verify this empirically, measurement of iSPs during sustained muscle activation or interhemispheric inhibition either at rest or during sustained isometric contraction may not be capturing an abnormally enhanced interhemispheric inhibition, which may be impairing the processes of initiating a useful movement after chronic stroke. It therefore is likely that the best approach by which to detect asymmetric interhemispheric inhibition after stroke is by applying the double coil method during production of a voluntary movement, where the active functional role of such inhibition is to prevent bimanual movements, and not when the limb is at rest.

Restoration of symmetry in interhemispheric connections and cortical excitability after stroke does not always predict functional improvement [90,91]. Those with large infarcts may instead show significant remapping of cortical representations to remote areas not normally involved in the lost function, a process known as vicariation [92,93]. The recently proposed 'Bimodal Balance-Recovery' model suggests that neither the interhemispheric imbalance model, nor the vicariation model, can predict recovery in all patients [94]. It proposes that if there is a high structural reserve, such as if some residual function remains due to partial retention of the integrity of the neural circuitry of the corticospinal tract, then the interhemispheric imbalance model will dominate and in these cases it may be beneficial to utilise therapies for rebalancing interhemispheric inhibition [95]. When structural reserve is low, vicariation will dominate, with more distant, even contralesional, areas recruited to take over lost function [93,94], which may explain why severely impaired patients often retain abnormal contralesional activation [96–98]. Thus in these cases, interhemispheric rebalancing may not be beneficial and these patients may benefit from facilitation of contralesional activity instead [95]. Utilising information about lesion size and corticospinal tract integrity will likely help in the stratification of patients towards therapies that are likely to be of most benefit for each individual [99]. Plow et al. (2016) suggest that neuromodulation techniques that boost plasticity based on the Bimodal Balance-Recovery model will result in better outcomes for patients, and are aiming to determine specific neurophysiological markers and cut-offs that may help to identify which patients will benefit from particular neuromodulation therapies. Clarification of these markers will certainly assist in determining the influence that interhemispheric imbalance has on functional recovery after stroke.

5. Current methods of neuromodulation to target interhemispheric inhibition

Understanding who is likely to benefit from 'rebalancing' therapies is an important first step towards raising the ceiling of maximum functional return that is currently reached through rehabilitation and spontaneous recovery. The next step for stroke survivors exhibiting a degree of interhemispheric imbalance amenable to therapy, is knowing how best to modulate excitability in the brain to accelerate and augment functional recovery. Neuromodulation through electrical or magnetic stimulation has offered much promise as techniques to augment stroke rehabilitation, however little is known of the effects of these therapies on brain circuits. Repetitive TMS or transcranial direct current stimulation (tDCS) are two non-invasive stimulation techniques that have been trialled clinically with the aim of modulating brain excitability in order to improve function following stroke [98,100]. The use of these stimulation techniques alongside or to 'prime' standard physical rehabilitation has become a large area of interest in the field, however there is still little consensus on the optimal stimulation paradigms or neuroanatomical targets to best maximise the benefits of rehabilitation.

Commonly, non-invasive brain stimulation is used over the ipsilesional hemisphere to enhance excitability in the peri-infarct tissue. Anodal (excitatory) tDCS over the affected hemisphere of

chronic stroke patients has been shown to transiently improve hand motor function on the Jebsen Taylor hand function test [2]. Similarly ipsilesional application of rTMS, either alone or combined with physical rehabilitation, has also been shown to enhance upper limb function with effects persisting from ten days to several months after the end of treatment [3–7,101]. Not all have seen success with this approach however. High frequency rTMS applied ipsilesionally alongside constraint-induced therapy did not enhance motor function [9] and has been shown to differentially affect cortical and subcortical stroke where it enhanced dexterity after subcortical stroke, but worsened dexterity after cortical stroke [102].

Another approach that has been utilised with some success is to down-regulate the excitability in the unaffected hemisphere, where excessive interhemispheric inhibition is said to originate [103,104], or to target interhemispheric inhibition directly [11]. Low frequency rTMS applied to the contralesional hemisphere can enhance various measures of paretic upper limb performance [7,105–111]. Additionally contralesional low-frequency rTMS can enhance L-IHI [11], and reduce the extent and duration of interhemispheric inhibition from the contra-to ipsilesional hemispheres [106,112,113] which correlates with rTMS-induced improvements in motor function [106,113]. Forms of TBS [114] have also commonly been applied using rTMS. Both intermittent theta-burst stimulation (iTBS) applied to the ipsilesional motor cortex [5,115], or continuous theta-burst stimulation (cTBS) applied to the contralesional motor cortex have been shown to improve paretic hand performance during a task, although contralesional cTBS has also been associated with reduced overall limb function [5].

It is important to note here that there are inconsistencies between studies investigating the effects of rTMS on motor function, or on physiological measures such as interhemispheric inhibition [8,116,117]. Not all studies demonstrate that rTMS can influence interhemispheric inhibition [52,118,119]. Indeed the effects of rTMS and TBS specifically have also been frequently shown to be highly variable between individuals [120,121]. Analysis of a large sample of participants has revealed that changing the orientation of the TMS coil delivering the stimulation produces different effects between individuals, possibly due to activation of different neural elements in each participant [122]. Alongside inter-individual variability, various studies have shown that the same TMS pulse can facilitate or suppress consequent cortical responses depending on the timing of the pulse relative to prior spontaneous or evoked brain activity [123,124]. Similarly, repeated application of the same tDCS protocols can induce opposing effects on motor cortex excitability depending on the time interval between the application of the different sets of stimulation [125]. These differences in prior brain-state and subsequent differences in homeostatic plasticity may therefore account for some of the inconsistencies between, or even within studies.

The vast parameter space of single or multiple stimulation patterns and sites, combined with the variability of neural responses in healthy individuals as a consequence of prior brain-states [123,124] make understanding the effects of rTMS in healthy individuals alone a daunting task. This is yet further amplified when attempting to use rTMS paradigms in stroke patients, who on their own represent a highly variable and heterogeneous population. This highlights a critical need for studies investigating the cellular mechanisms engaged by rTMS and how this may differ in the stroke-affected brain [126]. This should be followed by systematic investigations of how to optimise stimulation parameters for individuals before these approaches find their way into routine clinical practice for the treatment of stroke.

6. Novel methods of neuromodulation to target interhemispheric inhibition

Considering the inconsistencies of rTMS protocols, motor recovery following stroke might be enhanced using a therapy that does not attempt to grossly rebalance hemispheric excitability, but rather one that targets specific functional circuitry related to interhemispheric inhibition and movement activation. One approach is to drive passive movements of an affected limb via a device that is mechanically coupled to the movements generated in the other limb [127], essentially physiologically 'priming' specific motor circuits [53] instead of unfocussed global hemispheric priming using rTMS. This approach enhanced the rate at which patients reached their peak motor recovery post stroke, and the course of improvement correlated with progressive increases in interhemispheric inhibition from the peri-infarct area to the contralesional hemisphere [128]. In healthy individuals, passive mechanical coupling also leads to reduced interhemispheric inhibition from the active onto the passive hemisphere [53], and a short-lasting ($\approx$30 min) disinhibition of cortical areas representing the passive limb [53,129]. Interestingly this effect was most pronounced when symmetrical (mirror) movements were induced compared to asymmetrical movements. Collectively, this evidence suggests that focussed disinhibition may involve plasticity in transcallosal circuits normally specialised in preventing mirror movements. This short period of disinhibition may present a brief therapeutic window in which accelerated rehabilitation gains can be achieved, despite ongoing peri-lesional tonic inhibition. We propose that effective augmentation of stroke rehabilitation in cases where interhemispheric inhibition is dynamically enhanced requires targeted neuromodulation of the specific neural elements underlying interhemispheric inhibition.

Whilst not yet sufficiently developed for translation into human use, viral targeting and optogenetic modulation of specific interhemispheric circuits might present a novel way of specifically modulating the neural elements underlying abnormal interhemispheric inhibition after stroke [130]. The benefit of optogenetic stimulation is in the ability to selectively target particular neuronal projections, from within a specific brain nucleus. In comparison, the cellular effects of TMS or tDCS are much less focal, activating mixed populations of neurons and producing a range of effects that may ultimately cancel. Rodent studies have shown that precise activation of specific neuronal subtypes using optogenetics with patterns that mimic physiologically normal brain activity can enhance function in neurological disorders better than simple repetitive stimulation protocols [131]. If specific excitatory or inhibitory transcallosal circuitry were found to be abnormally active in animal models of stroke, theoretically the same circuitry could be identified and targeted in humans in order to optogenetically activate or inhibit this abnormal activity. The benefits of human translation of these optogenetic techniques are being discussed [132] and therefore may eventually become a powerful tool in the neuromodulation toolbox available to improve function in neurological conditions.

In the meantime, electrical stimulation using implanted electrodes may represent the most focal approach for brain stimulation of specific neural areas. In an animal model of interhemispheric inhibition, low-intensity TBS paradigms seemed to specifically target neural elements underlying interhemispheric inhibition. Specifically, electrical iTBS applied to the hemisphere contralateral to the recorded neuron via an implanted electrode, abolishes interhemispheric inhibition from the stimulated to the recorded hemisphere [51]. Low intensity electrical stimulation is known to activate low-threshold cortical neurons [37], thus in this context the targeted neural circuits might be those involved in inhibition

onto the recorded hemisphere. In a rat stroke model, iTBS applied at similar low intensities via an implanted contralesional electrode accelerated motor recovery (see Fig. 2B). Following three weeks of this electrical stimulation, limb function was 40% better than that measured in sham-stimulated rats [51]. Interestingly, low-intensity cTBS tended to impede recovery, raising the possibility that electrical cTBS, which potentiated monosynaptic connections from the stimulated cortex onto pyramidal cells in the contralateral motor cortex, may have also up-regulated inhibitory circuits (monosynaptic or polysynaptic) underlying interhemispheric inhibition, raising the threshold for activation of pyramidal motor neurons. Invasive stimulation of this nature may facilitate modulation of specific neuronal circuitry, in a more targeted manner than can be achieved using tDCS or TMS.

Invasive cortical electrical stimulation has been previously trialled in human stroke patients in the Northstar Neuroscience EVEREST Phase III trial. This trial attempted to enhance excitability in the surviving tissue in order to augment recovery from stroke and showed very promising Phase I and II results [133]. The Phase III trial failed to reach its primary efficacy end-point, however it was noted that extradural stimulating electrodes were not placed over viable tissue in many cases [134–137]. Post-hoc analysis revealed that in patients with stimulating electrodes placed over viable cortical tissue, 69% displayed a significant increase on the upper extremity Fugl-Meyer and Arm Motor Ability Tests at 4, 12 and 24-week assessment points compared with controls [138]. Whilst overall the EVEREST trial did not meet its primary end-point, this should not rule out more invasive stimulation methods as a potential option for some patients. Application of electrical stimulation to the contralesional hemisphere, where tissue still remains viable, may represent a method to dynamically modulate interhemispheric inhibition and normalise interhemispheric asymmetry when it is at its most disadvantageous following stroke, such as close to movement initiation [10]. An implanted electrode could facilitate longer or even continuous application of stimulation throughout activities of daily living, circumventing limitations of TMS, which currently requires costly external equipment, and application by a skilled operator.

7. Conclusions

Interhemispheric imbalance is one of the phenomena that could be targeted by neuromodulation following stroke to maximise recovery, and yet in only a proportion of patients the restoration of symmetry in interhemispheric communication appears to facilitate accelerated or enhanced recovery. Although previous studies have proven variable, we believe that future investigations should be designed with the assessment of interhemispheric inhibition made in the context of movement initiation in order to obtain a more meaningful picture of the negative impact of asymmetry on functional outcomes. We propose that interhemispheric inhibition in stroke recovery is a dynamic phenomenon strongly related to movement initiation, rather then one that remains static and persistently altered following stroke.

Modulating interhemispheric communication through invasive or non-invasive brain stimulation methods holds promise for augmenting rehabilitation therapy. However it is important to gain a greater understanding of the cellular mechanisms engaged by these treatments, since this will ultimately allow therapies to be more specifically targeted to the pathology affecting individuals. Well-designed animal experiments are tremendously valuable in this regard. Precise modulation of disrupted circuitry using more focal or specific neuronal targeting (including implanted electrical or optogenetic technology) may form the next generation of therapies for enhancing or accelerating recovery. Overall, modulation of interhemispheric inhibition after stroke alongside conventional rehabilitation does remain a potential avenue for therapy to allow the ceiling of stroke recovery to be raised.

Conflict of interest statement

The Authors declare no conflicts of interest.

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