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Motor cortex and motor cortical interhemispheric communication in walking afterstroke – the roles of TMS and animal models in our current and future understanding

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Abstract

Despite the plethora of human neurophysiological research, the bilateral involvement of the leg motor cortical areas and their interhemispheric interaction during both normal and impaired human walking is poorly understood. Using transcranial magnetic stimulation (TMS), we have expanded our understanding of the role upper-extremity motor cortical areas play in normal movements and how stroke alters this role, and probe the efficacy of interventions to improve post-stroke arm function. However, similar investigations of the legs have lagged behind, in part, due to the anatomical difficulty in using TMS to stimulate the leg motor cortical areas. Additionally, leg movements are predominately bilaterally controlled and require interlimb coordination that may involve both hemispheres. The sensitive, but invasive, tools used in animal models of locomotion hold great potential for increasing our understanding of the bihemispheric motor cortical control of walking. In this review, we discuss three themes associated with the bihemispheric motor cortical control of walking after stroke: 1) what is known about the role of the bihemispheric motor cortical control in healthy and post-stroke leg movements, 2) how the neural remodeling of the contralesional hemisphere can affect walking recovery after a stroke, and 3) what is the effect of behavioral rehabilitation training of walking on the neural remodeling of the motor cortical areas bilaterally. For each theme, we discuss how rodent models can enhance

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the present knowledge on human walking by testing hypotheses that cannot be investigated in humans, and how these findings can then be back-translated into the neurorehabilitation of post-stroke walking.

Keywords

Walking; interhemispheric motor cortical communication; stroke; rehabilitation; rodent models; translational science

Introduction

Six months after stroke onset, one out of four people require assistance with activities of daily living and one out three is unable to walk independently.¹ Two-thirds of people after stroke may experience critical limitations in functional walking and be at risk for additional declines in physical mobility and independent walking.² Impaired locomotion restricts a person after stroke from both performing mobility activities and participating in vocational and avocational activities. To rehabilitate post-stroke walking impairments, rehabilitation strategies³ have been developed to improve walking function and to promote greater participation in social activities. Yet, neither behavioral treatments, such as treadmill training, nor neurophysiological interventions, such as functional electrical stimulation, are capable of fully restoring walking to pre-stroke levels.⁴ The current therapies are likely less than optimal due, in part, to a lack in our understanding of the complex and inter-dependent neurophysiological processes involved in walking.

Human walking is a complex behavior resulting from integration of multiple structures and functions of the nervous system. Sensory feedback from the periphery, neural networks in the spinal cord, and descending control from brain areas contribute to the control of bipedal locomotion and the coordinated integration of these systems is responsible for the activation and modulation of motor neuron pools that innervate the active leg muscles.⁵ Damage to any of these systems can produce impairments in walking. A better understanding of each subsystem's role and how they work together is essential for understanding human locomotion and recovery of walking ability after brain damage.

One area of the neural control of human walking that remains under investigated is how the interhemispheric communication (IHC) between the motor cortex (MC) of each hemisphere may contribute to the coordination of walking in neurologically intact humans and to what extent alterations in IHC between ipsilesional and contralesional hemispheres may influence the coordination of walking after a stroke. The lack of complete understanding of the roles that MC and IHC plays in walking and walking recovery after a stroke, is in part, due to the lack of efficient tools to thoroughly investigate the functional capacity of MC during walking in humans.

In this review we will discuss three themes associated with the bihemispheric motor cortical control of walking after stroke in humans. For each theme we also will discuss the potentials of using rodent models to answer remaining questions derived from each theme that cannot be answered alone in humans. Then, we will advocate for the importance of the translation

to the neurorehabilitation of walking after stroke and discuss the practical considerations of using rodents, a quadruped walking model, to investigate the neural control of human walking, a bipedal walking model.

Interhemispheric Communication between the Leg Motor Cortical Areas

In humans, leg motor cortical areas are responsible primarily for inducing motor output to the contralateral leg muscles. Growing evidence indicates that the MC contributes to normal walking, both in animals^{6,7} and humans,^{8–10} Furthermore, the homologous leg motor cortical areas in each hemisphere communicate mainly with each other via callosal motor fibers located in the posterior limb and isthmus of the corpus callosum.¹¹ In neurologically intact brains, the IHC, which can be investigated using transcranial magnetic stimulation (TMS), is a balance between excitatory and inhibitory neural activation patterns.¹² Unilateral stroke affecting the upper-extremities alters this IHC balance,¹³ such that the ipsilesional cortex shows reduced excitability, while the contralesional cortex is overexcited during arm movements.^{14,15} Studies of the upper extremities have suggested that this abnormal decrease in IHC, mainly interhemispheric inhibition (IHI), is most commonly present in patients who have cortical stroke^{16,17} and high structural reserve¹⁸ and is related to poor motor outcomes in arm function.^{15,19}

It is possible that abnormal IHI is also related to greater impairments in the lower-extremities and contributes to impairments in walking. It can be difficult to separate normal from abnormal IHI. Unlike most upper-extremity functions, which are predominately unilateral and where IHC is better characterized, walking is a continuous bilateral motor action and requires interlimb coordination. During bilateral limb actions, the motor behavior of one limb has direct effects on the behavior of the contralateral limb.^{20,21} Stroke disrupts this interlimb interaction, and interlimb coupling is greatly degraded during bilateral tasks. Kautz and Patten²² demonstrated that the interlimb coupling quantified by the muscle activity of task-specific muscles in the legs was disrupted during cycling in people with chronic stroke, whereas the suppression of interlimb coupling was not detected either in isometric or discrete motor tasks. Similarly, Tseng and Morton²³ reported that in people with chronic stroke, limb coordination quantified by ankle kinematics and muscle activity of the medial gastrocnemius and tibialis anterior was significantly impaired during bilateral antiphase cyclic ankle movements. Conversely, this movement degradation was not significant during unilateral and bilateral in-phase ankle actions, regardless of whether the moving limb was either the paretic or the non-paretic limb.²³ The neuromechanical evidence from both studies suggests that a neural coupling exists between the limbs, and that stroke may degrade this interlimb coordination, which is present only during bilateral actions. Aberrant cortical IHI might explain, in part, these behavioral deficits in the interlimb coordination observed after stroke.

Paired-pulse TMS (ppTMS) can be used to investigate the role of MC and the communication between the two hemispheres, providing evidence for the role of IHC (inhibition and excitation) on motor function in both neurologically intact and clinical populations.¹⁸ IHC can be measured by the application of suprathreshold conditioning stimulus in one of the hemispheres, which generates an inhibitory effect on the

suprathreshold test stimulus applied to the contralateral hemisphere; the conditioning and test stimuli are separated by a variable interstimulus interval.²⁴ This noninvasive brain stimulation technique requires two TMS coils (eg, “figure-of-eight”), one coil per hemisphere, placed over the motor representation of the target muscle (eg, first dorsal interosseus) being examined.²⁴

Following a stroke affecting the upper-extremities, TMS has been used to demonstrate that IHC between arm regions of the MC is disrupted and may limit recovery of function.¹⁵ In contrast to upper-extremity investigations, lower-extremity measures of IHC between leg motor areas is limited due to their proximity in the MC. In humans, motor cortical representations of leg muscles (eg, tibialis anterior) lie close to midline, along the interior portion of the MC, folding into the medial longitudinal fissure (Figure 1).²⁵ TMS coils are relatively large, especially “figure-of-eight” and double-cone coils whose outer diameter can range from 70–120 mm, and positioning them adjacent to each other may make it impossible to stimulate bilateral leg motor cortical areas. For this reason, ppTMS is technically difficult, thus measuring the IHC between the leg motor cortical areas in humans has been limited.

In contrast to these limitations in humans, rodent hindlimb motor cortical representation is on the dorsal surface of the brain and lateral to the midline, and it may be more easily investigated using a small rodent TMS coil or intracortical microstimulation (ICMS).^{26–28} Two recent neurophysiological studies using ICMS techniques reported that the hindlimb motor area in rodents was, on average, 1–3.25 mm and 0.75–2.75 mm lateral to midline in rats²⁷ (Figure 2) and mice,²⁹ respectively. Following traumatic brain injury in rats, ICMS stimulation in the MC contralateral to the injury (the non-injured MC) elicited more ipsilateral hindlimb movements than sham operated (uninjured rats).³⁰ These data suggest that the shift in IHI may be quantifiable in rodents using ICMS. If so, then treatments or target therapies can be designed to investigate whether they have the ability to shift this pattern of contralesional MC-elicited impaired limb use that relates to greater deficits in walking, and if therapies can renormalize this aberrant activation.

Use of TMS in rodent models is feasible and reproducibly elicits electromyogram or mechanomyogram in the targeted extremity, either forelimb or hindlimb.^{31–37} For the rodent model, different protocols (eg, single pulse TMS, ppTMS) and applications (eg, diagnostic, therapeutic) of TMS have been tested and found to be useful for providing vital insights into the fundamental mechanisms of TMS.³⁸ Using one TMS coil (figure-of-eight with 50 mm coil diameter) over one MC, Luft et al.³⁴ demonstrated that it was possible to use common TMS procedures to obtain reliable bilateral hindlimb motor evoked potential (MEP) and recruitment curves, similar to those used in human TMS studies. Furthermore, the relative distance between the two hindlimb representations in the MC of rodents permitted the successful use of ppTMS to investigate the cortical inhibition mechanisms in rodents, demonstrating that it possible to induce IHI in both anesthetized³⁷ and unanesthetized³¹ intact rats from both the forelimb³⁷ or the hindlimb.³¹ One limitation to note is the large size of the TMS coil (eg, outside diameter: 40–70 mm) relative to the rat brain. Since it is not currently possible to have the spatial resolution that we do in humans, TMS current likely activates the entire rodent MC. These findings indicate that using ppTMS in rats may offer

another feasible technique to begin investigating the neural mechanisms and underlying structural and functional changes in IHC in intact and brain injured rat models.

TMS techniques may also be combined with existing research models to determine the role of interhemispheric interaction and to determine if IHI is mediated primarily via transcallosal fibers. Allred and colleagues³⁹ reported that intercortical connections via corpus callosum mediate some of the maladaptive effects of non-paretic forelimb training on the motor function of the paretic limb in a rat stroke model. In a series of studies, Allred et al.^{39,40} demonstrated that following a unilateral ischemic damage to the forelimb area of the sensorimotor cortex (SMC) damage, animals that receive unilateral reach training with the non-impaired forelimb (“good limb”) prior to rehabilitative reach training with the impaired forelimb (“bad limb”) have reduced recovery compared to animals that just receive impaired forelimb training. However, if following the unilateral stroke surgery and prior to “good” limb training the connections between the two SMCs are severed via callosal transections, then the good limb training no longer inhibits “bad limb” recovery.³⁹ This study further supports the potential role of the corpus callosum in interhemispheric interaction in motor behavior and may provide an experimental template, in conjunction with ppTMS, to test whether abnormal IHI leads to poor walking recovery and alters training induced neural plasticity. However, given that walking in rodents is a quadrupedal activity and it may be difficult to find as robust of an effect on recovery given that Allred et al.³⁹ also reported that if animals were given bilateral forelimb training prior to unilateral “bad limb” rehabilitative reach training, the maladaptive behavioral effects of bad limb training were not seen. The use of ppTMS, though, may be able to detect any potential increase in IHI and resulting alteration in neural functional or structural plasticity following ischemic damage to the hindlimb area of the SMC.

Neural Remodeling of Contralesional Hemisphere and Its Role during Walking

After stroke in humans, structural and functional plasticity occurs. This plasticity is usually adaptive, meaning that it can promote functional recovery or compensation.⁴¹ However, plasticity after stroke might be also maladaptive in that optimal recovery may be stymied by less optimal compensatory behaviors,^{42,43} such as Taub’s learned-disuse.^{44,45} Maladaptive plasticity may also result from functional and structural changes in that result in altered interhemispheric communication (ie, IHI) and the unmasking or increase in ipsilateral projections from the contralesional hemisphere to the paretic limb.⁴³ In people post-stroke, TMS stimulation of the contralesional MC can elicit ipsilateral responses in the paretic limb, a pattern of activation that is not as prominent in neurologically intact adults.⁴⁶ This altered activation of the paretic limb indicates the ability of the nervous system to reorganize the motor output from the contralesional hemisphere by unmasking uncrossed lateral corticospinal tracts (CST) projections^{46,47} and may facilitate some movement at the paretic limb. However, dominance of contralesional corticospinal connectivity of the impaired limb may limit long-term motor recovery.⁴¹ Consequently, restoring more balanced corticospinal connectivity between the ipsilesional MC and impaired limb may be crucial for the recovery of normalized interlimb coordination required for an optimal walking pattern. Furthermore,

rehabilitation strategies using neuromodulatory approaches (eg, repetitive TMS; rTMS) should perhaps focus on attenuating the altered corticospinal connectivity due to stroke (ipsilesional < contralesional) while promoting the normal premorbid corticospinal connectivity (ipsilesional > contralesional).

After stroke, use of ipsilateral projections from the contralesional MC during walking may hold more significance than during unilateral limb movements. As stated above, walking requires an interlimb coordination that implies that suppression and excitation of each hemisphere when it is in anti-phase mode with the contralateral hemisphere. After a unilateral stroke, the contralesional hemisphere might be required to be constantly excited in order to send neural input to the nonparetic and paretic leg via the crossed and uncrossed lateral CST, respectively. Studies of motor behavior showed that paretic leg movement was impaired when coupled with nonparetic leg movement,^{22,23} especially during anti-phase actions.²³ Several studies demonstrated the maladaptive effects of either increased activation in the contralesional hemisphere or corticospinal connectivity via uncrossed lateral CST. A functional MRI (fMRI) study in which people with chronic stroke executed passive and active dorsiflexion with the paretic ankle, showed that increased activation in the contralesional SMC and supplementary motor area correlated with increased disability, measured by the Motricity score.⁴⁸ Similarly, in studies using TMS, altered corticospinal connectivity from the ipsilesional and contralesional hemispheres to either leg was associated with slower walking speed and increased lower-extremity motor impairment (Fugl-Meyer assessment) in people with chronic stroke.⁴⁹ In addition, Madhavan and colleagues⁵⁰ showed that people post-stroke with prominent ipsilateral connectivity between the contralesional hemisphere and the paretic leg might be maladaptive for bilateral anti-phase mode goal directed ankle movements. This evidence indicates that walking may be negatively influenced by the maladaptive plasticity occurring in the contralesional hemisphere and the corresponding CST (ie, abnormal IHI and ipsilateral projections). However, these studies are limited by the difficulty in: 1) bilaterally measuring the relationship between corticospinal connectivity and walking-related, specific force generating muscles (ie, triceps surae) during walking;⁵¹ and 2) quantifying related structural neural plasticity.

Although the rodent ipsilateral CST is sparser than in primates,⁵² these uncrossed projections may still provide a template to examine their role in recovery from cortical damage. In rodent stroke models, neurophysiological measures⁵³ can be combined with neuromechanical measures^{54,55} and behavioral measures.⁵⁶ These models then can further investigate the structural and functional underpinnings for these neuromechanical and behavioral changes. For instance, people after stroke commonly shown an increased reliance on the non-paretic leg during the stance time,⁵⁷ but it is unknown whether this strategy is associated with structural plasticity in the contralesional hemisphere. If these studies can explain the underlying mechanisms of the effect of the contralesional hemisphere on walking, novel pharmacological, neurophysiological, and behavioral rehabilitation strategies can be developed and tested in clinical trials and then applied in clinical settings for targeting a functional walking recovery in people post-stroke. Findings from these studies will shed light on a topic that largely is neglected in both human and animal studies.

Effect of Walking Rehabilitation on Bihemispheric Neural Remodeling of Motor Cortical Areas

In humans, reorganization in the motor cortical areas and alterations in motor corticospinal excitability of leg muscles are reported after a form of walking-specific rehabilitation strategy post-stroke.^{58–61} In one study,⁵⁸ four people post-stroke received body weight-supported system treadmill training (BWSTT) for 10 weeks. By using an ankle dorsiflexion fMRI paradigm, findings demonstrated an activity-induced plasticity that was associated with functional improvements in behavioral measures, including increased walking speed, distance walked, and a greater Fugl-Meyer score.⁵⁸ The authors suggested that this paradigm could be used as an assay for walking-specific motor control in walking rehabilitation.⁵⁸ However, the sample size of this study was very small (N=12), so these results are by no means definitive. Similarly, Yen et al.⁵⁹ recruited 14 people post-stroke who were randomized to either the experimental group (BWSTT and physical therapy) or the control group (only physical therapy) and compared the area of TMS-evoked motor maps and motor corticospinal excitability of leg muscles. Only walking interventions induced functional plasticity in the brain (increase in the area of cortical motor map representation of tibialis anterior) and CST (decrease in motor threshold to evoke MEPs in tibialis anterior).⁵⁹ Miyai et al.⁶⁰ measured the cortical activity during treadmill walking in eight people post-stroke before and after inpatient rehabilitation via near-infrared spectroscopy. Results showed reduction in asymmetry of activation and increase in recruitment on motor-related brain areas.⁶⁰ Lastly, a recent randomized trial that combined a low-frequency rTMS over the contralesional hemisphere with task-oriented training⁶¹ found an increase in gait parameters, and a reduction in interhemispheric asymmetry of the amplitude of rectus femoris' MEP.⁶¹ The cumulative evidence from these studies points out that behavioral and neurophysiological interventions have the capacity to induce activity-dependent plasticity and can be used to alter MC related control of walking following stroke.

However, several gaps in our understanding remain. It is not clear how, or if, these interventions induce structural and/or functional remodeling in the MC and CST and alter communication between the two hemispheres. The existence of these gaps of knowledge in human studies is likely primarily due to the limited availability of invasive tools that can be used in humans, and careful examination in animal models of stroke might close these gaps.

Use of animal stroke models might be an excellent avenue for investigating bilaterally the neural functional and structural changes due to walking-specific rehabilitation interventions. In the last 20 years, numerous upper-extremity studies have employed animal stroke models and have shown that cortical plasticity occurs after forelimb training^{62–64} or limb immobilization⁶⁵ and that these changes are related to improved recovery.⁶⁶ Therefore, similar approaches can be utilized in rehabilitation of walking after stroke studies. For instance, animals with unilateral SMC lesion focused over the hindlimb area of the cortex could be trained to walk on motorized treadmills while receiving cortical stimulation, a modulator that is similar to rTMS in humans, either at ipsilesional, contralesional, or both hemispheres. Furthermore, both functional and structural changes can be examined in animal stroke models after walking-specific training by using different tools to determine

mechanisms underlying behavioral recovery and link these behavioral changes to structural and functional brain plasticity. Understanding the mechanisms could lead to new targets for adjunctive treatments that could be brought back to clinical trials.

Back-translation from rodent stroke models to walking neurorehabilitation in people post-stroke

Translation of knowledge gained from animal studies to clinical practice is not an easy or a fast task. The traditional model of the translational research used in stroke rehabilitation is unidirectional, but this approach has not been successful.⁶⁷ Conversely, bidirectional flow of knowledge between basic scientists and clinicians may improve and expedite the functional restoration of a motor task after a stroke, in this case walking.⁶⁷ This bidirectional relationship implies that scholars at both ends should be aware of each other's needs, share similar goals, and collaborate to set future directives.

One of the goals of this paper is to present some of the gaps in our understanding of the roles the MC and IHC play in the neural control of walking in people post-stroke so that these needs may be communicated to basic scientists to design and develop protocols and approaches for addressing hypotheses. Findings from subsequent animal stroke studies should translate into “proof-of-concept” human studies that can subsequently test the effect of these strategies in the field of motor control of walking and walking recovery after a stroke.

The translation of knowledge derived from the animal models can have significant clinical applications in the field of neurorehabilitation. In the past, for instance, findings derived from basic science studies carried out in animals led to the development of new neurorehabilitation treatments for the recovery of arm movements (eg, Taub's CIMT studies) and leg movements (eg, partial body weight support walking in spinal cats to body weight support treadmill walking).⁶⁸ Similarly, if rodent stroke models using the ppTMS paradigm show that abnormal IHI has a crucial effect on the bilateral control of locomotor behavior, “proof-of-concept” studies in humans should investigate how the reversal of IHI, which can be accomplished by using neuromodulatory cortical stimulation (eg, rTMS), can improve the coordinated control of walking after a stroke. Furthermore, if rodent stroke models determine to what extent the adaptations in contralesional hemisphere influence the bilateral control of walking, subsequent rodent studies should focus either on pharmacological, cortical stimulation, or cell replacement interventions that can attenuate these adaptations. Depending on the results from these studies, “proof-of-concept” human studies may attempt to replicate these approaches.

Practical Considerations

While we make a case for the use of quadrupeds, specifically rodents, to further investigate existing knowledge gaps about the role of bilateral MC in human locomotion, we appreciate that quadrupeds are an imperfect model of bipedal locomotion. One of the main differences between the two models is that quadrupedal rodent walking has wide base of support and low center of mass while the bipedal human walking has narrow base of support and high

center of mass. Therefore, the neuromechanical interactions during walking differ between the two models; others have tackled this debate directly, (see eg,⁶⁹ and⁷⁰). Furthermore, rodents have less similarities with humans in terms of behavior and sensorimotor integration, but they share many similarities with humans in terms of cerebrovascular anatomy and physiology.⁷¹ Further, it is unclear what the best experimental stroke model, although focal damage to the motor cortex or corpus callosum would provide the most direct way of investigating the roles of MC and IHC in post-stroke walking and recovery. Schaar et al. (2010) also provide a great review of available rodent behavioral tasks that are sensitive to impairments in locomotion which can be incorporated into future studies.

Despite of these considerations, rodent cortical stroke models can be of tremendous assistance in answering specific questions that cannot be answered in humans. Animal studies have been useful in furthering our understanding of the role MC plays in motor recovery of the upper-extremities following brain damage, providing a platform to develop potential prognostic tools to evaluate long-term outcomes and hypothesis driven investigation into putative treatments after stroke^{72,73} and other neurological injuries.⁷⁴ In this review we suggest investigating the interactions between homologous MC representational areas during coordinated use, as in locomotion, using animal models has some advantages and likely will lead to a better understanding of MC control of and IHC during walking. Lastly, though we focused on the role of MC during walking we do acknowledge that other brain structures (eg, brain stem) and descending pathways (eg, corticoreticular-reticulospinal) contribute to walking.⁷⁵

Conclusion

In this review, we discussed how using rodent models might shed light on the role of the bihemispheric motor cortical control during walking after stroke. Better understanding of the altered IHC after stroke may explain, in part, the behavioral deficits in the interlimb coordination during human walking observed after stroke. Use of ppTMS can assist in the investigation of the interaction between the homologous leg motor areas. In contrast to human leg motor cortical area, rodent brain, in which hindlimb motor cortical areas are more segregated than in humans, might be a good model for investigating the effect of IHC on walking behavior in both intact and stroke animals. Findings from these studies can then further elucidate functional and structural mechanisms underlying normal and post-stroke walking, while this deeper understanding of the MC role in walking may then be back-translated into better treatments to restore walking function, including using TMS to enhance rehabilitative interventions.

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Figure 1.

TMS-based optimal motor cortical locations and variations of the left and right abductor pollicis brevis and tibialis anterior in human healthy brains. Black dots denote the normalized hot spots while colored areas represent the 95% confidence intervals areas for the abductor pollicis brevis (left: red; right: dark blue) and tibialis anterior (left: green; right: light blue). (Used with permission from Niskanen E, Julkunen P, Saisanen L, Vanninen R, Karjalainen P, Kononen M. Group-level variations in motor representation areas of thenar and anterior tibial muscles: Navigated Transcranial Magnetic Stimulation Study. *Human brain mapping*. 2010; 31(8):1272–1280.)

Figure 2.

Motor organization of rat's brain using ICMS. A. The orientation of the location for the motor representations of the face, forelimb, and hindlimb on the dorsolateral part of the rat brain. B. ICMS-based hindlimb motor area in the left motor cortex of a representative rat. C. Individual ICMS-based hindlimb motor areas in 5 rats. (Used with permission from Frost SB, Iliakova M, Dunham C, Barbay S, Arnold P, Nudo RJ. Reliability in the location of hindlimb motor representations in Fischer-344 rats. *Journal of neurosurgery. Spine*. 2013; 19 (2):248–255.).