Gait improvement after treadmill training in ischemic stroke survivors

A critical review of functional MRI studies

Xiang Xiao¹, Dongfeng Huang¹, Bryan O’Young²

¹ Department of Rehabilitation Medicine, First Affiliated Hospital of Sun Yat-Sen University, Guangzhou 510080, Guangdong Province, China
² New York University School of Medicine, Rusk Institute of Rehabilitation Medicine/NYU Langone Medical Center, New York 10011, NY, USA

Abstract
Stroke survivors often present with abnormal gait, movement training can improve the walking performance post-stroke, and functional MRI can objectively evaluate the brain functions before and after movement training. This paper analyzes the functional MRI changes in patients with ischemic stroke after treadmill training with voluntary and passive ankle dorsiflexion. Functional MRI showed that there are some changes in some regions of patients with ischemic stroke including primary sensorimotor cortex, supplementary motor area and cingulate motor area after treadmill training. These findings suggest that treadmill training likely improves ischemic stroke patients’ lower limb functions and gait performance and promotes stroke recovery by changing patients’ brain plasticity; meanwhile, the novel treadmill training methods can better training effects.

Key Words
functional MRI; stroke; treadmill exercise; lower limb function; gait; ankle kinematics; cerebral plasticity; neurodegenerative disease; regeneration; neural regeneration

Research Highlights
(1) This paper summarizes the functional MRI changes in ischemic stroke patients after treadmill training with voluntary and passive ankle dorsiflexion. There are some changes in some regions of ischemic stroke patients including primary sensorimotor cortex, supplementary motor area and cingulate motor area after treadmill training.
(2) Treadmill training can influence the brain plasticity of ischemic stroke patients.
(3) Virtual reality-based treadmill exercise and the KineAssist are novel gait training methods. MRI-compatible device and tract-specific analysis may contribute to a better understanding of lower extremity motor control in persons after stroke.

Abbreviations
fMRI, functional MRI; ROIs, regions of interest; BWSTT, body weight-supported treadmill training; S1M1, primary sensorimotor cortex; FMA, Fugl-Meyer Assessment; SMA, supplementary motor areas; CMA, cingulate motor area; SII, secondary somatosensory cortex; M1, primary motor cortex; S1, primary sensory cortex; VR, virtual reality
INTRODUCTION

Many stroke survivors have residual gait impairment which includes slow walking speed, abbreviated paretic single limb support, increased step length, decreased hip flexion, increased knee flexion, and increased ankle plantarflexion at toe off\(^1\)\(^–\)\(^2\). A recent study suggests that if walking performance is poor, activities in the community will be limited in stroke survivors\(^3\). An important goal of post-stroke rehabilitation is to restore the ability to ambulate independently in the community which has been shown to require a velocity of 0.80 m/s\(^4\) and endurance to walk at least 367 m\(^5\).

The best way to improve walking after stroke is to walk\(^6\). Modern concepts of motor learning favor task-specific repetitive training. Repetition of an effective gait pattern is important to restoring gait function. Central neural plasticity is a likely mechanism underlying gait functional recovery after stroke. Task-oriented repetitive training such as treadmill exercise ought to be performed at speeds, and with limb kinematics that optimize what the locomotor networks can interpret as normal walking inputs\(^7\).

Functional MRI (fMRI) is one of the main tools to define brain functional responses and to follow-up on their evolution. It measures brain activation through changes in blood-oxygenation and flow. Several studies have related behavioral gains to changes within cerebral sensorimotor regions of interest (ROIs) over the course of treadmill exercise\(^8\)\(^–\)\(^11\). Ankle dorsiflexion is an important kinematic aspect of the gait cycle. The ankle paradigm may serve as a physiological assay of the optimal duration and intensity of treadmill exercise\(^10\). In this article, we review the literature on gait studies performed with fMRI before and after treadmill exercise.

TREADMILL EXERCISE AFTER STROKE

Current approaches in prescribing treadmill exercise parameters

Studies on body weight-supported treadmill training (BWSTT) have been initiated as early as 6 days after stroke\(^7\). Several randomized controlled trials have demonstrated benefits of treadmill exercise on various outcome parameters in stroke survivors with chronic gait impairments\(^8\)\(^–\)\(^15\). In a recent study, among 52 participants who received aerobic treadmill exercise, improvements in walking velocity were greater in those with more recent ischemic strokes\(^16\). Therefore, earlier intervention after the stroke may optimize treatment effects.

At the beginning of BWSTT, support from the harness was up to a maximum of 40% of body weight. During training, body weight support was reduced as soon as possible\(^17\). In most studies, treadmill velocity was adjusted according to a protocol described by Sullivan et al\(^18\), who recommended that participants practice ambulation on the treadmill at speeds above their preferred overground walking speeds, preferably at or above 2.0 mile/h (or 0.89 m/s). In a study by Franceschini et al\(^19\), treadmill velocity started from 0.1 m/s and aimed at ≥1.2 m/s according to the patient’s compliance.

Recently, “fast” treadmill exercise has been considered as an intervention that may improve walking speed of post-stroke patients to a greater extent than traditional programs that train at slower speeds. In a randomized controlled trial, patients after stroke walked on a treadmill at their fastest speed and the results showed a significant progression toward improved gait symmetry with increased speed. Significant improvements in paretic hip extension and knee flexion during swing were also found as treadmill speed increased\(^20\). Gait retraining using treadmill has shown efficacy. In previous studies, patients walked on a motorized treadmill for 10–60-minute periods 2 to 7 times a week for 2 weeks to 6 months\(^7\)\(^–\)\(^10\), 14, 21–27).

Effect of treadmill exercise on gait performance

Treadmill exercise is an intervention that improves walking speed and cardiovascular fitness in people who have had a stroke\(^8\)\(^–\)\(^14\), 16–18, 26–27). Treadmill exercise also facilitates practice of a more normal walking pattern\(^7\)\(^–\)\(^9\)\(^–\)\(^10\). The study performed by Dobkin et al\(^18\) with four chronic stroke survivors examined gait function during and after BWSTT. Walking speed, endurance (6-minute walk test) and the temporal features of gait improved significantly. Scores on the Fugl-Meyer Assessment (FMA) of the lower extremities improved as well. Enzinger et al\(^9\) investigated functional reorganization in 18 subcortical ischemic stroke survivors. Performance gains in walking speed and endurance (2-minute timed walk) were observed after the 4-week BWSTT.

Few studies investigated BWSTT in acute stroke. In a study, more normal ankle kinematics were observed in the BWSTT group. The BWSTT group also walked further and faster than the control group who received traditional gait training\(^7\).
EFFECT OF TREADMILL EXERCISE ON STROKE SURVIVORS USING fMRI

Treatment-induced cortical and subcortical reorganization occurs after ischemic stroke[28-31]. The neuroplasticity induced by treadmill exercise remains unclear. A recent study that used electroencephalogram (EEG) to record brain activity when healthy subjects walked on a treadmill found that at the end of stance phase, as the leading foot was contacting the ground, alpha- and beta-band spectral power increased in or near the sensorimotor and dorsal anterior cingulate cortex. In addition, intra-stride high-gamma spectral power changes were evident in sensorimotor, posterior parietal and anterior cingulate cortex. These findings demonstrate the cortical involvement in steady-speed human locomotion[32].

Using transcranial magnetic stimulation, Yen et al[15] found that the motor threshold for tibialis anterior in the unaffected hemisphere and map size for tibialis anterior in both hemispheres were significantly enlarged in the experimental group following additional BWSTT. Furthermore, correlations were shown between the improvements in TMS measures for tibialis anterior in the unaffected hemisphere and functional improvement. These results suggested that functional improvement may be partially due to the increase in excitability over the unaffected hemisphere.

To assess cortical and subcortical adaptations for the control of lower limb movements over the course of treadmill exercise, researchers have developed experimental designs to assess the motor representations of movements of the ankle with fMRI[9-11].

Relationship of ankle dorsiflexion and gait performance

An fMRI activation paradigm using ankle dorsiflexion has been shown to have face validity in the study of gait training. Adequate ankle control during gait is important for normal gait pattern. For foot clearance in stroke survivors, insufficient dorsiflexion increased the swing time of the affected leg[33]. A recent study confirmed that gait velocity and temporal asymmetry are affected by the strength of ankle dorsiflexors in patients after stroke[34]. Using near-infrared spectroscopic topography, a study found that ankle dorsiflexion generated a similar brain activation pattern to that associated with walking[35]. Dobkin et al[10] demonstrate that the neural control of walking in patients with stroke can be assessed indirectly by ankle dorsiflexion.

Patient-related issues

In a study by Enzinger et al[9], inclusion criteria for treadmill exercise included a score of ≥ 3 on the Functional Ambulatory Capacity rating scale. Patients with residual gait impairment attributable to ischemic stroke had to be able to dorsiflex the ankle by a minimum of 10°. Patients were excluded for the following reasons: cognitive impairment, extensive leukoaraiosis, other clinically significant causes for reduced mobility, rehabilitation within 4 months before inclusion, somatosensory or proprioceptive abnormalities, and any contraindications for MRI. Dobkin et al[10] chose patients with stroke who were able to dorsiflex the ankle by a minimum of 10°. Hemiparetic subjects received BWSTT and an fMRI study at the end of each block.

Several treadmill exercise studies with fMRI scanning in patients after ischemic stroke have been conducted recently[8-10]. Two main types of paradigms are used in fMRI studies, namely, block design and event-related design. In event-related design, the hemodynamic responses are evoked by repeated presentations of single stimulus, and the average transient response is calculated. Many functional neuroimaging studies used a block design, in which activations of brain regions are obtained by subtracting signal from blocks recorded in an “off” condition, from blocks recorded in an “on” condition[8-11, 36-39].

Previous experiments showed peak blood oxygen level-dependent (BOLD) signal changes of 1.04% and 0.89% for large and small dorsiflexion, respectively. In addition, graded dorsiflexion produced graded BOLD signals in primary sensorimotor cortex (S1M1) and supplementary motor areas (SMA) in healthy subjects[40]. Newton et al[41] found that ankle dorsiflexion was accompanied by extensor torques at the hip and knee. These subtle differences may result in differences in activity in the fMRI data between sessions. So the performance of motor task during fMRI should be fixed across all subjects as well as over time in studies for a sound result.

Dobkin et al[10] limited superior-inferior translation motion of ankle dorsiflexion by wearing a polypropylene ankle-foot orthosis. Subjects practiced two sets of dorsiflexor movements of 10°. For the passive movement paradigm, the assistant dorsiflexed the foot with one hand at the same rate and with the same visual cues viewed by assistants and subjects. The frequency and...
degrees of motion during ankle dorsiflexion were held constant for voluntary and passive movements.

In a study by Enzinger et al \[8\], ankle dorsiflexion were made in a purpose-built wooden apparatus. Active ankle dorsiflexion was paced by a visual cue. Passive movement of the ankle was conducted by the experimenter by 30°. Several sensorimotor ROIs participate in ankle dorsiflexion\[10]. These regions include contralateral and ipsilateral S1M1, SMA, cingulate motor (CMA), premotor cortex, prefrontal cortex, secondary somatosensory cortex (SII) and cerebellum. As shown in Figure 1, anatomic landmarks were applied to define these ROIs for each subject. The primary motor cortex (M1) was located in the posterior portion of the frontal lobe. The lateral postcentral gyrus was the location of the primary sensory cortex (S1). SMA was located on the midline surface of the hemisphere just anterior to leg representation of M1. CMA was defined by the cingulate cortex from the ascending branch of cingulate sulcus and behind the vertical plane passing through the anterior commissure. M1 works in association with other motor areas to plan and execute movements. Specific M1 neurons also represent the paraspinal muscles\[42]. S1 has a key role in storage and retrieval of representations of sensory information\[43]. The SMA may play a role in the direct control of movement. Prefrontal and premotor cortex may be important for purposeful modification of walking. SII connects to Brodmann area 3b, posterior parietal and prefrontal cortex. CMA may be important in the generation of choices and in monitoring their outcome. The cerebellum plays a leading role in regulation of postural control, execution of movement and motor skills configuration. In addition to ROI analyses, image data were analyzed using a voxel-based random effects model, in which voxel means volume pixel. This analysis investigated for differences in activation between groups without assumptions about the localization of ankle movement functions. The voxel-based analysis tested for activation changes throughout the entire brain, and provided locations of activation foci allowing for better anatomic correlation as compared with ROI analysis\[8].

In most studies, imaging data were analyzed using FSL or SPM. The numbers of voxels activated within each ROI were analyzed. Quantitative indices extracted from activation patterns, such as displacement of S1M1 coordinates, overactivation extent, the contrast in amount of activation between the unaffected and affected S1M1\[36], and the study of their changes over time have attracted considerable interests\[31, 45-48].

Brain activation during foot movements in patients with ischemic stroke

There are several studies using fMRI to define brain activities associated with ankle dorsiflexion in healthy subjects. One study exhibited a different activation pattern between lower limb joints in healthy subjects. The knee joint indicated a smaller MR signal change in the majority of ROIs in comparison with those from ankle and toes. The ankle and the toes showed a similar activation pattern across all ROIs, except for a few ROIs where the ankle presented a greater MR signal change in comparison with the toes\[36]. Ciccarelli et al\[37] found that passive movements of the ankle activated cortical regions similar in location to those activated by active movements in healthy volunteers. Active movements of both ankles generated greater activation than passive movements in ipsilateral M1 which had been identified in previous studies as being important for motor planning. Common activations during active and passive movements were found in the S1M1, premotor regions, and the subcortical regions, indicating that these regions participate in sensorimotor integration for ankle movements. Sahyoun et al\[38] found that active ankle movement was associated with larger activation with respect to passive movements in the postcentral gyrus. Frontal and association cortices were more active during anticipation (before passive movement) or preparation (before active movement) periods than during the movements themselves. This characterization of brain activation patterns associated with ankle movements in healthy volunteers as demonstrated through fMRI provides a promising application of fMRI as an outcome measure for the functional analysis of gait.

Dobkin et al\[10] presented control data for active ankle dorsiflexion. Activations were found in contralateral S1M1, SMA, CMA and premotor cortex, and ipsilateral cerebellum in healthy subjects. Voluntary movement...
produced more activation within S1M1 and SMA than passive ankle dorsiflexion. Four adults with chronic ischemic stroke activated fewer voxels at baseline with voluntary ankle dorsiflexion than normal subjects in S1M1. The three subjects with subcortical infarct evolved increases in counts within contralateral S1M1 and CMA by BWSTT, followed by declines as behavioral gains reached a plateau. For the subject with the frontal stroke, greater activity evolved the rim of the frontal infarct. The responses in SMA changed little over time. This study suggests that the ankle dorsiflexion fMRI paradigm can evaluate activity-induced plasticity during training to walk after stroke.

Enzinger et al. [39] observed neocortical activities associated with ankle dorsiflexion in patients with ischemic stroke. The extent of activation in the S1M1 and the SMA of the unlesioned hemisphere increased with disability. The changes were most prominent with the active dorsi- and plantarflexion. This may show mixed effects of a loss of normal interhemispheric inhibition of S1M1 and recruitment of motor control pathways from the SMA in the unlesioned hemisphere.

Enzinger et al. [39] also found that greater walking endurance was correlated with increased brain activities in the bilateral S1M1, the paracentral lobules, the CMA, and the caudate nuclei, particularly in the S1M1 after 4 weeks of BWSTT. This emphasizes the bihemispheric control of lower limb movement. A similar contrast for passive movement of the paretic ankle versus rest showed a significant correlation between performance gains and increased bilateral S1M1 activation. These results confirmed subcortical contribution to training-induced recovery of the lower limb function post stroke. In addition, a cortical modulation appears to be critically important in improving gait.

The above findings appear to fit into the model of an altered brain circuit linked to lower limb functional improvement after treadmill exercise on the basis of observations with knee movement fMRI paradigm. Exercise-mediated improvements in walking velocity associated with increased activation in cerebellum and midbrain during paretic knee movement. Other regions recruited after treadmill exercise during paretic knee movement included contralosional inferior parietal, lingual, parahippocampal and supramarginal gyr, ipsilesional postcentral and superior frontal gyri, and bilateral superior temporal gyrus. The results show that treadmill exercise activates neural networks in the cerebellum and cortical areas and midbrain that potentially mediate the improvements in gait elicited by treadmill exercise [6]. Miyai et al. [49] investigated how BWSTT affects cortical activation during gait using near infrared spectroscopy in patients with subcortical stroke. The task-related changes of S1M1 activation correlated with those of cadence. Improvement of asymmetry in S1M1 activation correlated with improvement of asymmetric gait after BWSTT.

Bipedal walking requires a highly integrated sensorimotor network. This network of spinal circuits, descending pyramidal, extrapyramidal, and brainstem controllers controls human walking [10]. The damaged adult human brain is able to compensate for motor deficits. The recovery likely occurs on the basis of reorganization of brain elements, such as axonal sprouting with formation of new synapses [50]. Shift or expansion of subcortical and cortical areas and cerebellum activation after BWSTT may reflect the disinhibition by the lesion of preexisting but normally inactive representations [51].

There are limitations in current fMRI studies of ischemic stroke patients. For example, fMRI activation paradigm using voluntary ankle dorsiflexion has focused on patients with good functions, because they were able to perform the motor tasks required for neuroimaging measurements [9]. However, patients with severe defects after ischemic stroke represent the largest fraction of the target population [9]. In addition, most fMRI studies that evaluated the effect of treadmill exercise on brain plasticity using a block design, although an event-related design might contribute to additional information.

NEW METHODS FOR GAIT TRAINING

Despite promising results, the personnel requirements necessary to provide treadmill exercise limit its application. Robotic devices that provide symmetrical assistance have been developed to facilitate treadmill exercise. Lokomat is limited to the sagittal plane, with restricted movement in the transverse and frontal planes. A recent study showed that walking speed, gait symmetry, lower extremity motor impairment (FMA), short physical performance battery, and balance (Berg Balance Scale) improved in the Lokomat group and only balance scores improved in the manual group [52].

Recently, body weight support was provided to people after stroke while they walked overground using a robotic
system. The KineAssist offers closed loop body weight support throughout the gait cycle. Subjects with post-stroke hemiparesis showed an average increase of 17% in overground walking speeds in the KineAssist when walking with some level of body weight support compared to the 0% body weight support condition[53]. More recent studies have focused on robotic devices for the ankle joint to address the problem of drop foot occurring during hemiparetic gait. For example, chronic stroke survivors walked overground and on a treadmill with and without the anklebot mounted on the paretic leg. The added anklebot had no significant effect on spatio-temporal parameters of gait in both overground and treadmill trainings[54].

In a randomized controlled trial, non-ambulatory persons after stroke, brain or spinal cord injury received two kinds of gait training: locomotor training with an electromechanical gait device and locomotor training with treadmill or task-oriented gait training. Gait ability (functional ambulation category) and gait velocity improved for all patients, but without significant difference between training types[55].

Virtual reality-based treadmill exercise
Virtual reality (VR) has been used in rehabilitation recently[31, 56]. VR uses simulation technology to create a graphic display with sounds and/or voices to engage subjects in a scenario in which they play a role. Kim et al[57] demonstrated that VR has an augmented effect on balance and locomotor recovery in patients with hemiparetic gait when added to conventional therapy. In a recent research, adults 1 year post-stroke accomplished 12 sessions of BWSTT with VR. The virtual environment shown on a screen in front of the treadmill gave participants the sensation of walking down a city street. Participants made significant improvements in the speed of overground walking speed, Functional Gait Assessment score and Berg Balance Scale score[25]. Yang et al[58] found that VR treadmill exercise improved balance skill in the medial-lateral direction better than traditional treadmill exercise did. In addition, they found VR treadmill exercise improved balance skill during sit-to-stand transfers more than the traditional one did.

Novel MRI-compatible device
In combination with a MR-compatible device enabling gait-like movements in a repetitive manner, fMRI can record brain activity during gait-like movements. Recently, a Magnetic Resonance Compatible Stepper is presented which can generate highly repetitive periodic active and passive leg movements comprised by hip, knee, and ankle joint displacements. This device may contribute to a better understanding of human gait control and related therapeutic effects in persons after stroke, and thereby, to improve training approaches[59].

Tract-specific analysis
Tract-specific analysis is a useful method to evaluate the fiber integrity of white matter tracts. A recent study investigated the intrarater and interrater reliability and validity of a tract-specific analysis for the corticospinal tract in patients with subcortical ischemic stroke. The results verified good reliability and validity of the tract-specific and ROI-based analyses of the corticospinal tract corresponding to lower extremity motor control in stroke survivors[60].

CONCLUSION
The literature overall suggests that it is possible to influence gait function after stroke by treadmill exercise and that training-induced brain plasticity is possible in ischemic stroke patients. Ankle dorsiflexion is a verified fMRI activation paradigm in parallel with greater motor control for walking. Furthermore, the change in gait function induced by treadmill exercise correlated with brain activities.

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