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Treadmill Exercise Activates Subcortical Neural Networks and Improves Walking After Stroke:

A Randomized Controlled Trial

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Abstract

Background and Purpose—Stroke often impairs gait thereby reducing mobility and fitness and promoting chronic disability. Gait is a complex sensorimotor function controlled by integrated cortical, subcortical, and spinal networks. The mechanisms of gait recovery after stroke are not well understood. This study examines the hypothesis that progressive task-repetitive treadmill exercise (T-EX) improves fitness and gait function in subjects with chronic hemiparetic stroke by inducing adaptations in the brain (plasticity).

Methods—A randomized controlled trial determined the effects of 6-month T-EX (n=37) versus comparable duration stretching (CON, n=34) on walking, aerobic fitness and in a subset (n=15/17) on brain activation measured by functional MRI.

Results—T-EX significantly improved treadmill-walking velocity by 51% and cardiovascular fitness by 18% (11% and −3% for CON, respectively; $P<0.05$). T-EX but not CON affected brain activation during paretic, but not during nonparetic limb movement, showing 72% increased activation in posterior cerebellar lobe and 18% in midbrain ($P<0.005$). Exercise-mediated improvements in walking velocity correlated with increased activation in cerebellum and midbrain.

Conclusions—T-EX improves walking, fitness and recruits cerebellum-midbrain circuits, likely reflecting neural network plasticity. This neural recruitment is associated with better walking. These findings demonstrate the effectiveness of T-EX rehabilitation in promoting gait recovery of stroke survivors with long-term mobility impairment and provide evidence of neuroplastic mechanisms that could lead to further refinements in these paradigms to improve functional outcomes.

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Disclosures
None.

Keywords

exercise; rehabilitation; plasticity; locomotion; fitness

Gait is a coordinated motor function fundamental to the conduct of activities of daily living. Human gait requires highly integrated sensory-motor control systems. The precise cortical, subcortical, and spinal control mechanisms of gait are not understood.[1] Ischemic stroke interferes with these neural control systems causing long-term walking impairment. The resulting physical inactivity and deconditioning accelerate the decline of neuromuscular function and fitness, increase the risk for cardiovascular disease, and propagate disability.

After stroke, brain physiology and organization are altered resulting in brain-activation patterns that are different from those of healthy individuals. During successful functional restoration these brain abnormalities either return to their normal state or undergo further change suggestive of compensation.[2] Task-specific rehabilitation can modify cortical circuitry to improve motor function after stroke in animals[3] and, upper extremity function in humans.[4] Functional MRI (fMRI) has demonstrated that bilateral repetitive arm-training recruits cortical areas in lesioned and nonlesioned hemispheres.[4] The cortex has a greater influence on arm than on leg control.[5] Walking is mediated by coordinated activity of networks involving cortical, subcortical, and spinal regions.[1,6] It is possible that repetitive gait training will modify these networks to improve ambulation,[7] but currently there is little evidence that brain plasticity underlies locomotor recovery after stroke in humans.[8]

The randomized controlled study reported in this article examines the hypothesis that a 6-month program of progressive task-repetitive treadmill exercise training (T-EX) improves fitness and gait function in subjects with chronic hemiparetic stroke by mechanisms of plasticity in specific cortical-subcortical networks. We compare 6 months of T-EX to a control program of standardized stretching tasks of equal in time and exposure to study staff. Stretching is a component of conventional physical therapy that is often prescribed for stroke patients to continue beyond the subacute phase of stroke to maintain flexibility and prevent contractures; however, it is neither aerobic nor requires as many active repetitions as T-EX.

Materials and Methods

Study Design

This single-center, randomized controlled trial investigated the effects of 6 month of T-EX on primary end points of ambulatory function (peak effort treadmill-walking velocity, overground-walking velocity during 6-minute walk and 10-meter walk) and cardiovascular fitness (VO_2 peak). The effects of T-EX on brain-activation and gait-recovery were assessed in a subset, ie, those participants who agreed and had no contraindications for fMRI (presence of metallic implants, claustrophobia or severe obesity). We enrolled men and women (older than 45 years of age) with chronic hemiparetic gait 6 or more months after their first clinical ischemic stroke after completion of conventional subacute rehabilitation. Subjects were recruited from the Baltimore Veterans Affairs Medical Center and the University of Maryland-Lawrence J. Kernan Rehabilitation Hospital. The study was approved by the institutional review boards of the University of Maryland, Baltimore Veterans Affairs Medical Center, and Johns Hopkins University. All participants provided written informed consent.

Baseline evaluations included medical history and physical examination, ECG, blood chemistries and hematologic examination, Folstein Mini-Mental State examination (MMSE), and Center for Epidemiological Studies Depression Scale (CES-D). Participants with heart failure, unstable angina, peripheral arterial occlusive disease, dementia (MMSE $\leq$23 for those

with 9th grade education or more and ≤17 for those with 8th grade education or less), significant aphasia (unable to follow 2-point commands), untreated major depression (CES-D ≥16), and other medical conditions precluding participation in aerobic exercise were excluded. Gait-safety and cardiopulmonary response to strenuous physical exertion were assessed during a screening treadmill exercise test. Subjects achieving adequate exercise intensities (walking for at least 3 minutes at a minimum of 0.09 m/s) without signs of myocardial ischemia or treadmill exercise intolerance were enrolled.

Randomization

Subjects were randomized to 6-month T-EX or a control standardized stretching (CON) program of frequency and duration equal to T-EX that did not to have the amount of task-repetition and gait-specificity of T-EX but which provided the same level of interaction with study staff. Randomization was performed using a stratified block allocation scheme (variable block size, allocation ratio 1:1). A computer-based pseudorandom number generator and the Moses-Oakford assignment algorithm were used to develop the randomization schedule. Because age and severity of gait deficit may affect response to intervention, the randomization was stratified based on age (<65 versus ≥65 years) and self-selected over ground-walking speed (<0.44m/s versus ≥0.44m/s).

Primary End Points: Measures of Ambulatory Function and Cardiovascular Fitness

At baseline, 3 and 6 months, maximum walking velocity and VO_2 peak were measured during a symptom-limited maximal effort treadmill exercise test. Overground-walking ability was evaluated by a 10-meter walk at fastest comfortable pace. Ten meters is a distance equal to that associated with home-based activities.[7] At baseline and 6 months walking capacity required for more sustained tasks of daily life was assessed by a 6-minute walk at the subject's fastest comfortable pace. Investigators administering these tests (F.I., L.F.) were blind to group assignment.

Secondary End Point: fMRI

Walking cannot be studied directly during fMRI; consequently, single-joint movements of the lower extremity were used to detect brain-activation changes in studies of neural control of the legs.[9,10] We studied knee motion because many subjects used ankle splints during T-EX because of a foot-drop (Table 1); therefore, the ankle was not uniformly trained. Cortical-activation during knee movement in fMRI shows similarities to activation patterns observed during walking.[5,6,11]

fMRI was performed at the Kirby Center, Kennedy Krieger Institute, Baltimore, within 2 weeks of the start and end of training using a 1.5T system (Philips). Brain-activation during unilateral knee movement was measured as previously described.[12] After knee-movement practice (10 repetitions), 2 functional scans were performed measuring brain-activation during movement of the nonparetic knee followed by the paretic knee. For each functional scan a total of 60 axial blood oxygenation level dependent (BOLD)–weighted scans (echo planar imaging, TR 3 seconds, TE 40ms, slice thickness 5 mm, 30 sections) covering the entire brain to the level of the pons were acquired during 3 imaging cycles. Each cycle consisted of 10 scans during rest followed by 10 scans during knee movement. Knee extension against gravity was controlled to minimize the possibility that altered movement after training would induce changes in fMRI activation patterns. Knee flexion-extension, performed at a constant rate (0.33 Hz), was cued by acoustic signals and was performed within 30° and 15° relative to standard anatomic position. Each subject's range of motion during imaging was set at baseline, was the same at baseline and 6 months, and was the same in the paretic and nonparetic legs.

Participants wore a vest connected to a support that stabilized their torso, supported their legs and immobilized the thigh to minimize head motion artifacts. Prespecified exclusion criteria for head motion artifact were presence of head movement on video and >3 mm head motion (in any direction) detected using the motion correction analysis in SPM5 (www.fil.ion.ucl.ac.uk/spm/software/spm5).

Optical switches recorded knee movement onset and return times. The times did not change from baseline to 6 months suggesting comparable movement dynamics (paired *t* tests: T-EX, extension P=0.36, flexion P=0.71; CON, extension: P=0.58, flexion: P=0.68). Video-monitoring allowed for assessment of compliance and for detection of overt head motion. No subject had visible cocontraction of both knees, either at baseline or 6 months. A T1-weighted image set was acquired for anatomic localization (3D-MPRAGE sequence, resolution 1 mm^3). Investigators administering fMRI tests (F.V., A.L.) were blind to group assignment.

Interventions

The T-EX training goal was three 40-minute exercise sessions per week at an aerobic intensity of 60% of heart rate reserve. Duration and intensity started low (10 to 20 minutes, 40% to 50% heart rate reserve) and increased approximately 5 minutes and 5% heart rate reserve every 2 weeks as tolerated. To reach intensity targets, treadmill velocity and incline were increased by 0.05 m/s and 1% increments, respectively. Subjects randomized to CON performed 13 supervised traditional stretching movements on a raised mat table with a therapist's assistance as previously described.[7] Each movement was performed actively if possible or passively with a therapist's assistance. Movements included quadriceps, calf, hip and hamstring stretch, low back rotation and stretch, chest stretch, bridging, shoulder shrug, abduction, and flexion, heel slides and short arc of quadriceps. The duration of each CON session and the number of sessions were equal to the T-EX sessions.

Statistical Analyses

Primary End Point Analysis—Separate repeated measures ANOVAs, one for each of the 4 primary outcome measures (maximum walking velocity and VO_2 peak during a treadmill stress test, and maximum comfortable walking velocity during a 10-meter walk and a 6-minute walk), were used to determine the effect of intervention on outcome. Independent variables included group (T-EX, CON), time (2 dummy variables representing baseline, 3 months, 6 months) as well as a group by time interaction. Three covariance structures—unstructured, compound symmetry, and 1st order autoregressive—were used to account for the serial autocorrelation of repeated values from the same subject. AICC, a modified version of Akaike information criterion, was used to select the best structure.[13] To determine whether age, time since stroke, sex, side of stroke, or lesion location (subcortical, cortical, brain stem) predicted outcome, each of these variables was added to the models described above. Each variable was tested in a separate model.

fMRI Analyses (ROI-based)—Brain-activation in the individual subject was measured in prespecified regions of interest (ROI) that were selected at the beginning of the study from the Automated Anatomic Labeling (AAL) atlas[14] based on a priori knowledge of brain-activation during gait and knee movement in healthy hemiparetic subjects.[5,11,12] These ROIs included cerebellum anterior, cerebellum posterior, supplementary motor area, midbrain, and sensorimotor cortex. The mean parameter estimates reflecting the difference in BOLD signal between knee movement versus rest were derived for all voxels within each ROI that passed a significance threshold of P<0.001, uncorrected for multiple comparisons.

These values, determined for each individual at baseline and postintervention, were used as dependent variables in within-group and between-group analyses.[15] Separate models were

computed for the paretic and nonparetic legs and for each ROI. Independent variables included "side of ROI" (ipsilesional versus contralesional) and group (T-EX versus CON). Two-way interactions were included and removed if $P>0.05$. Dependent variables were either "brain-activation per ROI" for within-group tests or the difference of post minus pretraining activation per ROI for between group analyses.

Pearson correlation coefficients and probabilities were computed to test for a relationship between the changes in peak treadmill-walking velocity and fMRI-activation in the ROIs. For all analyses, primary end point and fMRI (ROI-based), a 2-tailed $P<0.05$ was considered significant.

fMRI Analyses (voxel-based)—In addition to ROI analyses, image data were analyzed using a voxel-based random effects model across all subjects. This analysis tested for differences in activation between groups without a priori assumptions about the boundaries of brain anatomy or localization of gait/knee movement functions. The voxel-based analysis, therefore, tested for activation changes throughout the entire brain, not only in ROIs and provided precise locations (atlas coordinates) of activation foci thereby allowing for better anatomic correlation as compared with ROI analysis. Using SPM5 and standard protocols (www.fil.ion.ucl.ac.uk/spm/software/spm5), individual parametric contrast maps testing for increased activation between time points were computed (2-session fixed effects or "1st level" model). These contrast maps were then used in a "2nd level" random-effects model to detect differences between groups.[15] A probability threshold of $P=0.05$ corrected for multiple comparisons using a false discovery rate procedure was used to generate group-difference maps. To evaluate the relationship between the changes in brain-activation and peak treadmill velocity, the 1st level contrast maps were entered into a random effects regression model (all subjects) using the difference in post/pretreadmill-walking velocity as covariate.

Results

Recruitment and Baseline Characteristics

A total of 71 subjects completed the study between 2003 and 2006, 37 T-EX and 34 control subjects. Thirty-two participated in the fMRI study (15 T-EX, 17 CON, Figure 1). Drop-out rates were 35% and 39% during T-EX and CON, respectively, within the range of comparable exercise studies.[7,16] T-EX and CON groups in either the full dataset or in the fMRI subset were similar in demographic (Table 1) and baseline walking function variables (Table 2). Likewise, the fMRI subset was similar to the entire cohort (Tables 1 and 2). Training compliance (attended sessions/planned sessions) was 89% for T-EX and 85% for CON groups.

Primary End Points

T-EX produced a 51% increase in peak effort treadmill walking velocity that was significantly greater than the 11% increase in CON (T-EX, baseline → 3 months → 6 months: 0.77, 0.64 to 0.90 m/s, mean, CI → 1.00, 0.84 to 1.15 m/s → 1.11, 0.95 to 1.27 m/s, CON: 0.79, 0.64 to 0.93 m/s → 0.84, 0.68 to 1.01 → 0.88, 0.71 to 1.05 m/s; group × time effect: $P<0.001$; Figure 2). The average walking velocity during a 6-minute overground walk increased by 19% in T-EX (0.55, 0.45 to 0.65 m/s →0.63, 0.52 to 0.73 m/s) and by 8% in CON (0.55, 0.44 to 0.65 m/s →0.57, 0.46 to 0.69 m/s; group × time effect: $P=0.030$, Figure 2). Fastest over ground walking velocity in 10m walks increased with T-EX (0.72, 0.59 to 0.85 m/s → 0.82, 0.69 to 0.95 m/s) 2-fold more than in CON (0.66, 0.54 to 0.79 m/s →0.71, 0.58 to 0.84 m/s), 14% versus 7%, but the difference did not reach significance (group × time effect: $P=0.28$, Figure 2). Peak effort VO_2 increased by 18% in T-EX (12.9, 11.5 to 14.3 mL/kg/min → 14.1, 12.4 to 15.9 mL/kg/min → 15.2, 13.5 to 16.8 mL/kg/min) and decreased in CON (12.9, 11.5 to 14.4 mL/kg/min→12.8, 10.9 to 14.6 mL/kg/min→12.5, 10.7 to 14.2 mL/kg/min); this difference between

groups was significant (group × time effect: $P<0.001$, Figure 2). If the 2 types of primary end points (walking and fitness) are corrected for multiplicity, the between-group changes in peak effort treadmill velocity ($P<0.001$) and VO_2 peak ($P<0.001$) remain significant, only 6-minute walk becomes insignificant, but still showing a trend ($P=0.06$).

Between group changes in peak effort treadmill walking velocity, VO_2 peak or 6-minute walk velocity were neither predicted by age ($P=0.85$, $P=0.53$, $P=0.47$ for peak treadmill velocity, VO_2 peak and 6-minute walk velocity, respectively), time since stroke ($P=0.63$, $P=0.97$, $P=0.18$), side ($P=0.39$, $P=0.93$, $P=0.89$) nor location of the lesion ($P=0.57$, $P=0.37$, $P=0.27$). Only sex had a significant effect on change of VO_2 peak (2.9 mL/kg/min lower in women than men $P=0.003$). Improvement in peak treadmill velocity was predicted by baseline peak treadmill velocity ($P<0.001$). Neither of the other end point variables was predicted by its baseline value (VO_2 peak $P=0.75$, 6-minute walk velocity $P=0.82$).

Fifteen T-EX and 17 control subjects with no metal implants or claustrophobia were eligible for and underwent fMRI. In this subset significant between-group differences in favor of T-EX were found for peak effort treadmill walking velocity (group × time effect: $P<0.001$; 48% increase in T-EX, 11% in CON) and peak effort VO_2 (group × time effect: $P=0.029$; 16% increase in T-EX, 1% in CON). A trend was present for an improvement in 6-minute walk velocity (group × time effect: $P<0.068$; 17% increase in T-EX, 3% in CON); fastest overground walking velocity in 10 m walks increased by 21% in T-EX and 5% in CON, but between group comparisons were insignificant ($P=0.17$). Hence, the magnitude of change across 6 months in walking function and fitness in the subset receiving fMRI was equivalent to the entire cohort for both T-EX and CON groups.

Functional MRI

Brain-activation in the posterior lobe of the cerebellum increased in T-EX but not in CON with a significant between-group difference ($P=0.005$, Table 3). Activation in the midbrain increased in T-EX, decreased in CON and the difference between groups was significant ($P<0.001$, Table 3). For the nonparetic limb, decreased activation was found within both groups for certain ROIs but no between group differences were present (Table 3). Interactions between group and side of ROI as well as main effects of side of ROI were insignificant and excluded from all models.

Voxel-based analyses identified voxels with significant differences in activation change between groups, ie, a baseline to post-training change in T-EX but not in CON (Table 4). Such voxels were found in posterior cerebellum and in bilateral red nucleus reflecting the between-group differences in activation change in midbrain and posterior cerebellar ROIs described above. Other regions recruited after training during paretic limb movement in the T-EX but not the CON group included contralesional lingual, parahippocampal, inferior parietal and supramarginal gyri, bilateral superior temporal gyrus, and ipsilesional postcentral and superior frontal gyri (Figure 3A). Ipsilesional supplementary motor area and contralesional precuneus and cingulum increased in activation during nonparetic knee movement (Table 4). There were no regions where activation was decreased after T-EX.

Relationship of fMRI to Behavioral Ambulatory Outcomes

Using data derived from ROIs, there was a positive correlation between change in treadmill-walking velocity and increase of activation in the contralesional posterior cerebellum (T-EX: $r=0.54$, $P=0.037$, but not for CON, $r=0.11$, $P=0.68$) and the midbrain (all subjects combined: $r=0.50$, $P=0.005$, but not within T-EX $r=0.29$, $P=0.29$ or CON $r=-0.13$, $P=0.64$). No significant correlations between walking velocity and fMRI activation were observed for other ROIs. Using the image data (voxel-based analysis), a random effects regression model

identified areas in the contralesional posterior cerebellum and lingual gyrus, bilateral superior temporal gyrus and ipsilesional middle frontal gyrus (Brodmann area 6) where the intervention-related (T-EX and CON) increase in activity during paretic knee movement correlated directly with a change in treadmill walking velocity (Figure 3B).

Discussion

This randomized controlled study shows that repetitive gait training on a treadmill improves fitness and walking and recruits neural circuitry in midbrain and cerebellum as well as in frontal, temporal and parietal cortical areas in chronically hemiparetic stroke survivors. Subcortical recruitment was associated with increases in treadmill-walking velocity. Brain adaptations did not occur in circuitry controlling the nonparetic leg after T-EX, and were not present in either leg in a control group subjected to stretching tasks. The observed changes in regional brain-activation suggest there are putative neuroplastic mechanisms by which T-EX restores locomotor capacity and functional gait abilities in hemiparetic stroke.

Treadmill exercise combines active repetition, task-specificity, and proprioceptive entrainment with aerobic exercise. The first 3 may mediate faster and more efficient gait, which together with aerobic exercise increases cardiovascular fitness and contributes to further augmentation of ambulatory function.[7] Our results show that T-EX activates networks in the cerebellum and midbrain and cortical areas that potentially mediate the improvements in ambulation elicited by treadmill training.

Upper extremity movement–learning is mainly linked to cortical plasticity,[17–19] although cerebellum and basal ganglia may undergo short-term adaptations in early learning phases.[19] While recovering upper extremity function after stroke, several studies indicate increased bilateral-activation followed by reductions in brain-activation ("focusing") during the months after the event.[20] For locomotor recovery, a decrease in contralesional cortical-activation was accompanied by an increase in ipsilesional activation.[21] We did not observe reductions in cortical-activation after 6 months of TM potentially reflecting the fact that subcortical instead of cortical networks are involved in mediating T-EX effects. In contrast to cortical networks, subcortical regions show increases in activation during recovery: increased activation in the contralesional cerebellum has been linked to better recovery in a sample of 12 stroke survivors.[22] The increased activation in subcortical regions found here with T-EX may point to enhanced signaling in 2 candidate neural circuits.

One circuit consists of the red nucleus (RN), cerebellum and inferior olive. Via projections to RN this circuit receives input from cortex. It may provide timing cues and corrective signals necessary for coordinated phasic movements and movement learning.[23] A role for the RN in walking is substantiated in studies of nonhuman primates where RN stimulation evokes locomotion,[24] and in cats where RN seems to contribute to interlimb coordination.[25] In a mouse model of stroke, locomotor recovery was associated with sprouting of fibers between cortex and bilateral RN.[26] In addition to generating motor output, the rubrocerebellar circuit and the somatosensory cortex are active during somatosensory discrimination tasks, thus suggesting a role in sensory processing.[27] The processing and relay of somatosensory information to the motor cortex are required for successful movement learning.[28] Thus, consistent with findings in animal models T-EX may induce adaptations in RN that could improve walking by enhanced integration of somatosensory information into locomotion.

The second candidate circuit consists of cerebellum and the midbrain locomotor region that is part of the reticular formation in the immediate vicinity to RN (limitations of fMRI spatial resolution do not allow for a separation). The midbrain locomotor region receives neural signals from basal ganglia and cortex. Together with the cerebellum, the midbrain locomotor region

activates spinal locomotor pattern generators via the pontomedullary reticular formation.[29] Our findings could be interpreted as an activation of this pathway by T-EX to promote locomotor relearning.

The recruitment of either circuit was specific for paretic limb movement after T-EX and did not occur in the control group, which received comparable attention but no form of highly repetitive, bilateral exercise. In healthy humans cerebellar-activation increases between imagining to walk and to run suggesting that faster locomotion required greater input from cerebellar and midbrain locomotor centers.[30] This is congruent with our finding in stroke survivors. Whether the enhanced recruitment of these networks reflects structural reorganization of cortico-subcortical circuitry remains to be tested by studying the long-term retention of these neuroplastic changes or by studies of brain morphology.

Locomotor disability diminishes physical activity, placing the stroke patient in a vicious cycle in which immobility promotes deconditioning, sarcopenia and metabolic dysfunction that can increase cerebrovascular risk and further worsen disability.[31] The absolute gain in $V0_2$ peak of 2.3 mL/kg/min with T-EX is clinically significant; fitness gains approximating one metabolic equivalent (3.5 mL/kg/min) were found to prospectively predict 17% to 29% reductions in nonfatal and 28% to 51% reductions in fatal cardiac events.[32] The absolute improvements in treadmill speed of +0.23 m/s in T-EX versus +0.05 m/s in CON translate into a substantial improvement of short distance walks (+0.1 m/s in T-EX) whereas CON subjects do not show a meaningful change in ambulatory speed (+0.04 m/s).[33] The 30 m absolute improvement in endurance 6-minute timed walks after T-EX is a change that is between “small meaningful” (20 m) and substantial (50 m) compared to the negligible changes in CON (7 m).[33] By dually benefiting cardiovascular fitness and neuromotor function, T-EX has the potential to improve the ambulatory function of stroke survivors, to reduce insulin resistance and to reverse glucose intolerance to lower subsequent cerebrovascular risk[31,34] and improve long-term cardiovascular health outcomes.[32]

This is the first randomized trial to examine the brain mechanisms underlying locomotor adaptations to task-repetitive lower extremity treadmill exercise training in a disabled population with neurological impairments caused by stroke. There are some limitations involving methodology and study design that should be considered. fMRI measures brain-activation indirectly through changes in blood-oxygenation and flow. Hence, intervention-related factors or pathology related to generalized vascular disease may have affected blood flow and confounded the results. However, the involvement of a control group consisting of patients with similar disease and disability and reporting group differences, minimizes this potential confound.

The main purpose of the control group was to provide attention, patient involvement, and exposure to the training environment and staff equal in time to T-EX. It did not permit a definitive conclusion that brain adaptations are specific to T-EX. From the perspective of the fMRI findings, such a conclusion would require the addition of studies involving the comparison of T-EX to a different training method that produces identical functional improvements or testing a healthy population. Further research is needed to elucidate the specific contributions of aerobic fitness, neuromuscular mechanisms and nervous system plasticity to the health benefits of treadmill exercise after stroke.

Summary

This randomized controlled study provides the first evidence that, as predicted from animal studies,[3,35] there is increased activation of cortico-subcortical networks produced by task-repetitive treadmill exercise training of chronic stroke survivors. Subcortical networks could

be a site of plasticity or compensatory activation, and their recruitment may be one mechanism by which T-EX improves walking in hemiparetic stroke. It is promising that T-EX can stimulate new or underused brain circuits and improve ambulation in stroke survivors even after completion of conventional rehabilitation therapy.

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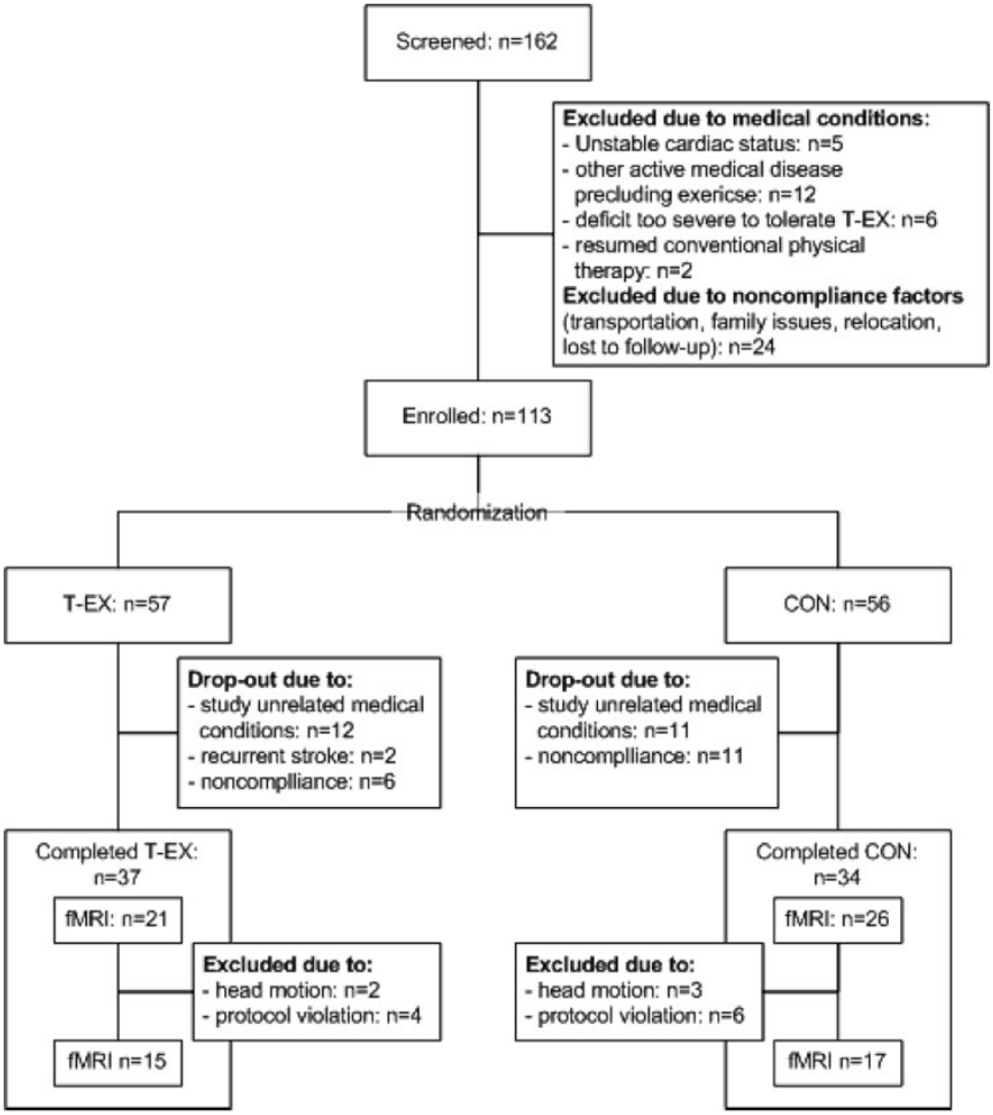

Figure 1.
Participants flow through the trial.

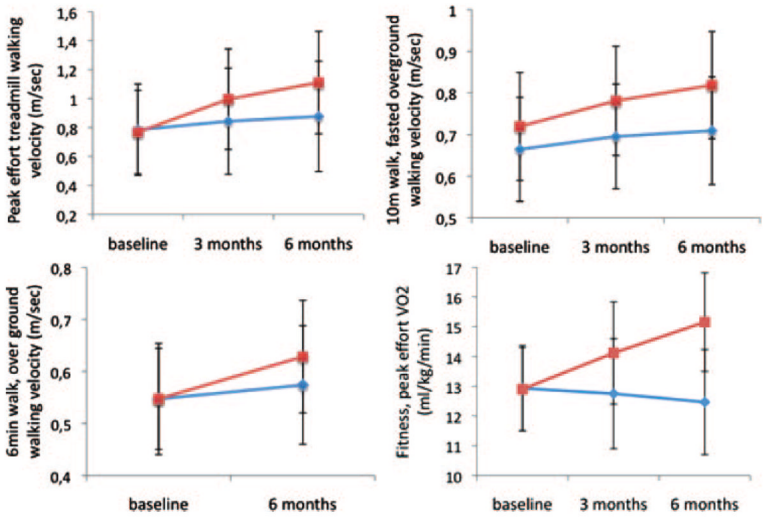

Figure 2.
Primary end points. Changes in measures of walking function and fitness in T-EX versus CON groups for the entire dataset (for statistical differences see text, error bars represent CI).

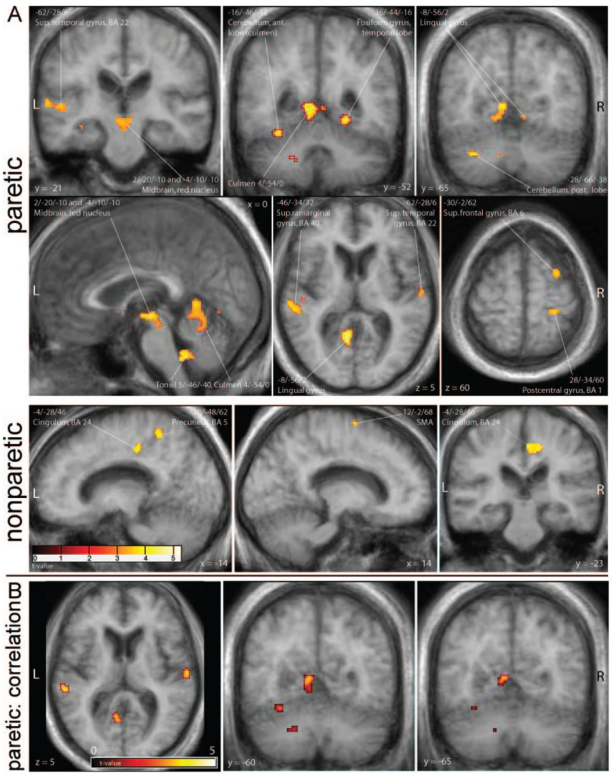

Figure 3.

Cohort fMRI maps (voxel-based analysis). (A) showing brain regions where activation during paretic knee movement increased after T-EX training compared to stretching CON. Colored regions indicate areas with a statistically significant increase over time that was different between groups, the equivalent of a group * time interaction ($P<0.05$, random effects model, corrected for multiple comparisons, coordinates reference to the Montreal Neurological Institute reference brain). (B) showing brain regions where the change in activation occurring over the course of intervention (T-EX and CON subjects combined) correlates with the postpre difference in treadmill walking velocity (random effects factorial regression model, $P<0.001$ uncorrected).

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Table 1

Baseline Characteristics

	All Patients		Patients With fMRI		
	CON (n=34)	**T-EX (n=37)**	**CON (n=17)**	**T-EX (n=15)**	**Comparison Between Full Dataset and fMRI Subset (*P*)**
	Mean or n (SD or %)	**Mean or n (SD or %)**	**Mean or n (SD or %)**	**Mean or n (SD or %)**	
Age (years)	63.6 (10)	63.2 (8.7)	63.2 (9.4)	64.3 (9.8)	0.76[*]
Time since stroke (months)	44.6 (18.8–70.5)[†]	62.5 (36.0–88.9)	56.8 (5.2–108.4)	63.9 (36.3–91.6)	0.51[*]
Sex					0.29[‡]
Female	20 (59%)	18 (49%)	10 (59%)	11 (73%)	
Male	14 (41%)	19 (51%)	7 (41%)	4 (27%)	
Race[§]					0.06[¶]
Black	18 (53%)	20 (54%)	11 (65%)	11 (73%)	
White	15 (44%)	15 (41%)	6 (35%)	4 (27%)	
Hispanic	0 (0%)	1 (3%)	0 (0%)	0 (0%)	
Other	1 (3%)	1 (3%)	0 (0%)	0 (0%)	
Location of stroke lesion[‖]					0.84[¶]
Cortical (with or without subcortical)	12 (35%)	9 (24%)	6 (35%)	3 (20%)	
Subcortical	13 (38%)	19 (51%)	9 (53%)	9 (60%)	
Brain stem	7 (21%)	5 (14%)	2 (12%)	3 (20%)	
Unknown	2 (6%)	4 (11%)	0 (0%)	0 (0%)	
Side of stroke					0.53[‡]
Right	21 (62%)	13 (35%)	8 (47%)	6 (40%)	
Left	12 (35%)	21 (57%)	9 (53%)	9 (60%)	
Unknown	1 (3%)	3 (8%)	0 (0%)	0 (0%)	
Assistive device					0.24
None	14 (41%)	13 (35%)	8 (47%)	5 (33%)	
Quad-point cane	5 (15%)	9 (24%)	1 (6%)	5 (33%)	
Single-point cane	13 (38%)	12 (32%)	8 (47%)	3 (20%)	
Walker	1 (3%)	3 (8%)	0 (0%)	2 (13%)	
Wheelchair	1 (3%)	0 (0%)	0 (0%)	0 (0%)	
Prior rehabilitation (inpatient & outpatient weeks)	15.2 (2.2)	12.9 (1.8)	18.0 (3.0)	17.0 (3.0)	0.52[*]

	All Patients		Patients With fMRI		
	CON (n=34)	T-EX (n=37)	CON (n=17)	T-EX (n=15)	Comparison Between Full Dataset and fMRI Subset (*P*)
	Mean or n (SD or %)	Mean or n (SD or %)	Mean or n (SD or %)	Mean or n (SD or %)	
NIH Stroke Scale	3.6 (2.9)	3.5 (3)	2.6 (2.7)	3.8 (2.3)	0.34
History of myocardial infarction					0.17‡
No	29 (85%)	33 (89%)	17 (100%)	14 (93%)	
Yes	5 (15%)	4 (11%)	0 (0%)	1 (7%)	
History of diabetes mellitus					0.25‡
No	29 (85%)	25 (68%)	16 (94%)	11 (73%)	
Yes	5 (15%)	12 (32%)	1 (6%)	4 (27%)	
History of hypertension					0.62‡
No	8 (24%)	8 (22%)	5 (29%)	4 (27%)	
Yes	26 (76%)	29 (78%)	12 (71%)	11 (73%)	
Betablocker treatment					0.81‡
No	24 (71%)	29 (78%)	14 (82%)	11 (73%)	
Yes	10 (29%)	8 (22%)	3 (18%)	4 (27%)	
Smoking					0.90¶
Current	5 (15%)	1 (3%)	1 (6%)	1 (7%)	
Former	20 (59%)	22 (59%)	11 (65%)	7 (47%)	
Never	8 (24%)	12 (32%)	4 (24%)	5 (33%)	
Unknown	1 (3%)	2 (5%)	1 (6%)	2 (13%)	
Body mass index (kg/m^2)	28.3 (6.3)	28.9 (6.3)	28.8 (7.7)	29 (5.7)	0.76*

** t* test,

† interquartile range,

‡ Fisher exact test,

§ by self report,

¶ Mann-Whitney *U* test,

|| cortical strokes include those affecting sensorimotor cortex and/or other cortical areas.

Table 2

Baseline Functional Assessments

	All Patients		Patients With fMRI		
	CON (n=34)	T-EX (n=37)	CON (n=17)	T-EX (n=15)	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Comparison Between Full Dataset and fMRI Subset (*P*)
Walking velocity during 6 minutes timed walks (m/s)	0.53 (0.28)	0.55 (0.3)	0.59 (0.3)	0.53 (0.25)	0.58*
Walking velocity (fastest) during 10 m walks overground (m/s)	0.66 (0.33)	0.74 (0.4)	0.73 (0.29)	0.67 (0.32)	0.98*

* *t* test.

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Table 3

Change in Brain-Activation by ROI

	T-EX		CON		
	% Change (SE)	**Within Group *P* Value***	**% Change (SE)**	**Within Group *P* Value***	**Between Group Difference *P* Value†**
Paretic limb					
Cerebellum (anterior lobe)	25 (17)	**0.039**	20 (15)	0.35	0.13
Cerebellum (posterior lobe)	72 (21)	**0.004**	8.1 (12)	0.66	**0.005**
Midbrain	18 (10)	**<0.001**	−40 (12)	**0.004**	**<0.001**
Precentral/postcentral gyrus	15 (14)	0.65	17 (12)	0.10	0.13
SMA	4.3 (9.3)	0.74	3.2 (12)	0.65	0.81
Supramarginal gyrus (BA40)	7.3 (14)	0.59	9.3 (9.4)	0.59	0.56
Nonparetic limb					
Cerebellum (anterior lobe)	−19 (13)	0.21	−19 (14)	0.12	0.91
Cerebellum (posterior lobe)	−17 (11)	0.48	−19 (10)	0.36	0.70
Midbrain	−32 (8.5)	**0.037**	−61 (8.6)	**<0.001**	0.77
Precentral/postcentral gyrus	2.3 (14)	0.84	−26 (10)	**0.026**	0.47
SMA	23 (23)	0.34	−20 (12)	0.13	0.14
Supramarginal gyrus (BA40)	−18 (14)	0.25	−25 (8.4)	0.41	0.59

*Effects of time in within group models,

†effect of group on the change in fMRI activation (difference post/pre).

BA indicates Brodmann's area; SMA, supplementary motor area.

Table 4

Voxel-Based Analysis, Regions of Activation Change

Limb	MNI Coords			Side Relative to Stroke	AAL/TD Lobes (TD)
Paretic	−8	−56	2	Contralesional	Lingual gyrus
	2	−20	−10	Ipsilesional	Midbrain (red nucleus)
	−4	−18	−10	Contralesional	Midbrain (red nucleus)
	−18	−40	−6	Contralesional	Parahippcampal gyrus
	−16	−46	−12	Contralesional	Culmen/cerebellum anterior lobe
	−28	−66	−38	Contralesional	Crus 1/cerebellum posterior lobe
	36	−44	−16	Ipsilesional	Fusiform gyrus/temporal lobe
	5	−46	−40	Midline	Cerebellar tonsil
	4	−54	0	Midline	Culmen
	−62	−28	6	Contralesional	Superior temporal gyrus
	62	−18	4	Ipsilesional	Superior temporal gyrus
	−46	−34	32	Contralesional	Supramarginal gyrus
	−44	−38	52	Contralesional	Inf. parietal gyrus
	28	−34	60	Ipsilesional	Postcentral gyrus
	30	2	62	Ipsilesional	Superior frontal gyrus
Nonparetic	12	−2	68	Ipsilesional	SMA
	−10	−48	62	Contralesional	Precuneus/Parietal lobe
	−4	−28	46	Contralesional	Mid cingulum/Frontal lobe

Center voxels of brain areas with significant between group differences in activation change (voxel-based models, *P* threshold <0.05, corrected for multiple comparisons).