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Research article

Structural and functional improvements due to robot-assisted gait training in the stroke-injured brain

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HIGHLIGHTS

- Robot-assisted gait training may be promising for post-stroke rehabilitation.
- The supplementary motor area of the unaffected hemisphere had increased FA.
- Intact supplementary motor areas may be facilitated by robot-assisted gait training.

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ABSTRACT

Robot-assisted gait training (RAGT) can improve walking ability after stroke. Because the underlying mechanisms are still unknown, we analyzed changes in post-stroke injured brains after RAGT. Ten non-ambulatory patients receiving inpatient rehabilitation were examined within 3 months of stroke onset. RAGT consisted of 45 min of training, 3 days per week. We acquired diffusion tensor imaging (DTI) data before and after 20 sessions of RAGT. Fractional anisotropy (FA) maps were then used to determine neural changes after RAGT. Fugl-Meyer motor assessment of the lower extremity, motricity index of the lower extremity, functional ambulation category, and trunk control tests were also conducted before training, after 10 and 20 RAGT sessions, and at the 1-month follow-up. After RAGT, the supplementary motor area of the unaffected hemisphere showed increased FA, but the internal capsule, substantia nigra, and pedunculopontine nucleus of the affected hemisphere showed decreased FA. All clinical outcome measures improved after 20 sessions of RAGT. Our findings indicate that RAGT can facilitate plasticity in the intact supplementary motor area, but not the injured motor-related areas, in the affected hemisphere.

1. Introduction

The recovery of walking function after stroke is a main goal of rehabilitation, which primarily utilizes neuroplastic changes to restore function. Thus, one important goal of rehabilitation is to effectively use neuroplasticity for such recovery [4,23]. One method of enhancing neuroplasticity is the repetitive practice of specific functional tasks; this repetition is a key principle of rehabilitative therapy [4,17]. For the specific recovery of walking, repetitive gait training can produce modest improvements [10].

Robot-assisted gait training (RAGT) can provide more supportive repetitive task-specific training and even produce independent walking [10,14,25]. Indeed, previous studies in patients with stroke showed that RAGT can improve functional ambulation category (FAC) or other clinical scores (i.e., walking ability) [14,20,25].

Abbreviations: RAGT, robot-assisted gait training; DTI, diffusion tensor imaging; FA, fractional anisotropy; FAC, functional ambulation category; FMLE, Fugl-Meyer motor assessment of the lower extremity; MI, motricity index of the lower extremity; TCT, trunk control test; SMA, supplementary motor area; PPN, pedunculopontine nucleus; CR, corona radiata; PCC, posterior cingulate cortex; MCA, middle cerebral artery; unaffected, unaffected hemisphere; affected, affected hemisphere; MNI, Montreal neurological institute; R, right; L, left; Days, days poststroke; T0, before training; T1, after 10 sessions; T2, after 20 sessions; T3, 1-month follow-up; UH, unaffected hemisphere; AH, affected hemisphere.

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However, no studies have clarified brain structural changes after RAGT in such patients.

Human locomotion is controlled by complex systems. Although the underlying mechanisms regulating these systems are largely unknown, repetitive gait training appears to act mainly at the level of spinal and supraspinal pattern generators [5,25]. With these considerations in mind, we aimed to identify changes in the injured brain after RAGT in a group of patients with supratentorial stroke. To this end, we analyzed diffusion tensor imaging (DTI) data simultaneously with gait improvement.

2. Materials and methods

2.1. Subjects

Ten patients (9 men, 1 woman) with stroke were recruited using the following criteria: (a) first ever unilateral stroke confirmed by magnetic resonance image (MRI) or computed tomography; (b) supratentorial stroke within the last 3 months; (c) FAC of ≤ 3 (FAC 5: ambulates on stairs and inclines; 4: ambulates on level surface; 3: ambulates with one person on standby; 2: requires intermittent support; 1: requires continuous support; 0: cannot ambulate or requires more than one person's help) [13]; (d) at least 18 years of age; and (e) cognitive function sufficient to allow cooperation. Exclusion criteria were: (a) progressive or unstable stroke or (b) coexisting neurological and/or orthopedic disease that could impair locomotion. The study (NCT02569190; ClinicalTrials.gov) was approved by our Institutional Research Ethics Committee for Human Subjects. Informed consent was obtained from all patients.

2.2. Study design

The study design is outlined in Fig. 1. A prospective open-label study was performed. RAGT consisted of 45 min of gait training with Walkbot (P&S Mechanics, Seoul, South Korea), 3 days per week for 20 sessions. Clinical outcomes were evaluated before training (T0), after 10 and 20 sessions (T1 & T2), and at 1-month follow-up exams (T3). Clinical outcome measures included Fugl-Meyer motor assessment of the lower extremity (FMLE) [11], motricity index of the lower extremity (MI), FAC, and trunk control tests (TCT). MRI data were acquired before (T0) and after 20 RAGT sessions (T2).

2.3. Robot-assisted gait training

Walkbot (P&S Mechanics, Seoul, South Korea) is a robotic-driven gait orthosis for control of posture, a body-weight support system, and a treadmill [3]. A suspension vest and harness connected to a counterweight system provide lumbopelvic stability and body weight support [16]. These were placed on the patient, and then the patient's hip, knee and ankle joint axes were consistently positioned with the exoskeletal orthosis for adjustment of joint movements at individualized gait speeds. As function improved, the treadmill speed was increased to a maximum of 2.2 km/h, with the level of assistance by the exoskeletal orthosis maintained at 100% throughout all sessions.

2.4. MRI acquisition

All images were acquired with a 3 T clinical whole-body MR scanner (Siemens, Erlangen, Germany) using a 20-channel head coil. High-resolution 3D T1-weighted images and DTI were obtained before training (T0) and after 20 sessions of RAGT (T2). The 3D T1-weighted image parameters were: TR/TE = 1900/2.57 ms, matrix = 256 × 256, field of view = 230 × 230 mm^2, flip angle = 9, and slice thickness 1 mm. DTI parameters were: TR/TE = 9700/92.0 ms, matrix = 112 × 112, field of view = 224 × 224 mm^2, NEX = 1, 30 directions, b = 1000 s/mm^2, and slice thickness 2 mm.

2.5. Imaging preprocessing

Visual inspection of all diffusion-weighted images was conducted. For each subject, diffusion-weighted images were registered to the corresponding b = 0 image with an affine transformation to correct distortions due to eddy current (FSL 4.1; http://www.fmrib.ox.ac.uk/fsl). Fractional anisotropy (FA) maps were constructed in native space using the Diffusion Toolkit.

A voxel-based method similar to voxel-based morphometry was used to preprocess FA values using SPM12 [24]. To create a lesion-overlapping map and conduct statistical comparisons, b = 0 and FA images of 3 patients with left-hemisphere lesions were flipped to locate the lesion area within the right hemisphere. After flipping images, two-step registration was applied to normalize individual FA maps to the standardized space. FA maps were coregistered to individual b = 0 (non-diffusion-weighted) images for each timepoint. Then, b = 0 images were registered to the standard Montreal Neurological Institute template provided by SPM12. The transformation matrix from native space to standardized space was applied to coregistered FA images. The normalized FA images of all participants were then averaged and smoothed to create a new study-specific template. Finally, FA maps were re-registered to the study-specific template and smoothed with a Gaussian kernel of 4 mm full-width at half-maximum. The smoothed images were used for further statistical analysis.

2.6. Statistical analysis

We tested effects of RAGT on brain structure by paired sample *t*-tests implemented in SPM12. Statistical comparisons of FA values before and after RAGT at each voxel were conducted. The significance was set at an AlphaSim corrected $p < 0.05$, which corresponds to uncorrected $p < 0.005$ and $k = 34$. The cluster size, k, was determined by Monte Carlo simulations (10,000 iterations).

Analyses of clinical outcome measures were performed using SPSS version 20 (IBM, Chicago, IL, USA). Friedman's test with post-hoc (Dunn's procedure) was applied to reveal the effects of RAGT on clinical outcome measures [8]. The significance level was $p < 0.05$.

3. Results

3.1. Sample characteristics

The age (mean ± SD) of the patients was 67.6 ± 9.3 years (range = 48–83 years), and time since stroke was 34.8 ± 27.6 days. Nine patients had ischemic stroke, and one patient had a hemorrhagic stroke. Seven strokes occurred in the right hemisphere, and three occurred in the left hemisphere. The mean FAC score was 1.7 ± 1.3 and mean FMLE was 16.4 ± 7.8 (Table 1). Fig. 1 summarizes the lesion data.

3.2. Lesion size and overlap across participants

The individual lesion sizes are summarized in the last column in Table 1. The lesion overlaps across the subjects are illustrated in Fig. 2. The maximum overlap of the lesions occurred in the putamen of the affected hemisphere, though almost all areas in the hemisphere were affected. Six patients out of the group of 10 showed an impact lesion in the region of the putamen.