Neural Plasticity

Neurorehabilitation: Neural Plasticity and Functional Recovery

Guest Editors: Toshiyuki Fujiwara, Nam-Jong Paik, and Thomas Platz

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Editorial Board

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Editorial

Neurorehabilitation: Neural Plasticity and Functional Recovery

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Neurorehabilitation plays an important role for neural plasticity and functional recovery following neurological disease. Neurorehabilitation is based on rehabilitation medicine, neuroscience, and neurophysiology. This special issue focused on the efficacy and mechanism by which neurorehabilitation can induce neural plasticity and functional recovery.

Articles published in this special issue covered neurorehabilitation following stroke, spinal cord injury, and other neurological disorders.

T. Fujiwara et al. reviewed the neurorehabilitation using electromyography- (EMG-) controlled neuromuscular electrical stimulation for upper extremity motor function following stroke. This review showed that application of wearable EMG-controlled NMES for 8 hours in daytime improved both arm and hand function and can induce plastic change in intracortical interneuron and spinal reciprocal interneuron.

J. Fu et al. reviewed the functional recovery induced by the exercise after spinal cord injury. Therapeutic exercise can induce reshaping of the skeletal muscle, physiological change of spinal motor neuron, and remodeling of the motor cortex.

Neurophysiology and neuroimaging are great tools for revealing neural plasticity induced by neurorehabilitation.

Neuroimaging studies in this special issue revealed novel findings of cortical reorganization following spinal cord injury, facial nerve palsy, hearing loss, and aerobic exercise in older adults.

Neurophysiological studies in this special issue revealed neural activity related to reduction of gait speed in Parkinson's disease and functional recovery of hemiplegia following stroke.

Advanced neurophysiological and neuroimaging techniques provided new insight into the functional recovery in neurological disorders.

We hope this special issue provides further knowledge of neurorehabilitation.

Toshiyuki Fujiwara
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Clinical Study

Changes in Cortical Activation Patterns in Language Areas following an Aerobic Exercise Intervention in Older Adults

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Previous work has shown that older adults who evidence increased right inferior frontal gyrus (IFG) activity during language tasks show decreased sematic verbal fluency performance. The current study sought to evaluate if an aerobic exercise intervention can alter patterns of brain activity during a semantic verbal fluency task assessed by functional magnetic resonance imaging (fMRI). Thirty-two community-dwelling, sedentary older adults were enrolled to a 12-week aerobic "Spin" exercise group or a 12-week nonaerobic exercise control condition (Balance). Thirty participants completed their assigned intervention (16 Spin; 14 Balance) with pre- and postintervention assessments of a semantic verbal fluency task during fMRI and estimated VO_2max testing. There was a significant increase in the change scores for estimated VO_2max of the Spin group when compared to the Balance group. Semantic verbal fluency output within the scanner was also improved in the Spin group as compared to controls at postassessment. Group fMRI comparisons of IFG activity showed lower activity in the right IFG following the intervention in the aerobic Spin group when compared to the Balance group. Regression analysis of imaging data with change in both estimated VO_2max and semantic verbal fluency was negatively correlated with activity in right IFG. The current work is registered as clinical trial with NCT01787292 and NCT02787655.

1. Introduction

Over the past few decades considerable attention has been devoted to examining the benefits of aerobic exercise on central nervous system plasticity. Aging research suggests that the positive effects of aerobic exercise involve higher order cognitive-executive processes, which are subserved largely by the frontal lobes [1–3]. Significantly, the frontal structures and related executive processes required for semantic verbal fluency are among the areas demonstrated to be most affected by aerobic exercise in humans [1, 4]. For example, Baker et al. (2010) reported that older participants with mild cognitive impairment who participated in an aerobic exercise regimen had improvements in semantic fluency, as assessed by the Delis-Kaplan Executive Function (DKEF) category test when com-pared to a contact controlled cognitive training group. Additionally, Voelcker-Rehage et al. [5] studied executive function in older adults engaging in a walking exercise program for one year. Participants in the aerobic exercise condition evidenced significant improvements in both category member generation and visual search acuity. In our own lab, a recent study demonstrated improvements in semantic verbal fluency in previously sedentary older adults following 12-week of aerobic, "Spin" cycling when compared to a control group [6]. A noted limitation in that study was our inability to identify the neural underpinnings promoting the semantic verbal fluency gains associated with increased cardiovascular fitness brought on by the aerobic exercise intervention. As such, we designed the current study to attempt to elucidate the neural mechanisms that may underlie improvements in semantic output associated with improved cardiovascular fitness in older adults.

Aerobic exercise has been increasingly associated with improvements in memory, executive function, and patterns of neural activity as assessed by fMRI [2–4, 7–11]. Recent fMRI evidence has also indicated that increased levels of

aerobic capacity in older adults are also associated with improvements in language function and a more efficient neural recruitment array during a semantic verbal fluency task. For example, in a cross-sectional study, Zlatar et al., 2013, demonstrated that the neural recruitment array during a semantic verbal fluency task in physically active older adults resembled that of younger adults, while sedentary older adults showed decrements in suppression of areas that should be inhibited during the task. They went on to demonstrate that longer interhemispheric inhibition, as measured by transcranial stimulation, was associated with more negative task-related activity in the right and left posterior perisylvian cortex, suggesting that sedentary aging may result in losses in task facilitatory cortical motor inhibition [11]. As such, based on these findings, the losses of negative task-related activity may be mitigated by regular engagement in physical exercise [12, 13]. This indicates that older sedentary adults may be exhibiting a loss of inhibition associated with younger adults and physically active older adults (see also, [14]). However, as previous studies of exercise and language function have primarily been of a cross-sectional nature, we currently know little about how aerobic exercise interventions affect the neural substrates of semantic verbal fluency in previously sedentary older adults.

The aims of the present study were to test the effect of a 12-week aerobic exercise intervention against a nonaerobic control condition to investigate changes in semantic verbal fluency and its underlying neural activity in previously sedentary older adults. We hypothesize that increased aerobic capacity brought on by the aerobic exercise intervention will be associated with decreased blood oxygenation level dependent (BOLD) activity in right lateral frontal regions (Broca's homologue). Specifically, we hypothesize that the aerobic intervention would result in a decrease in recruitment of Broca's homologue which would correlate with behavioral improvement in a semantic verbal fluency language task.

2. Methods

2.1. Participants. In this 12-week randomized controlled trial, 32 participants were divided into an aerobic, Spin exercise group (Spin; $n = 17$) or a nonaerobic control group (Balance; $n = 15$) to equalize contact and monitoring. Study personnel explained the purpose, potential risks of the experiment and completed the informed consent process with each participant following protocols approved by the Emory University's Institutional Review Board (IRB) in compliance with the Helsinki Declaration.

Participants in this study were recruited from a volunteer database, which included elderly individuals (60 years and over). To meet inclusion criteria participants had to (1) be between 60 and 89 years of age, (2) report being sedentary, defined as not engaging in structured physical activity and/or not accumulating 30 minutes or more of moderate physical activity most days of the week, (3) have no history of depression, neurological disease, including Parkinson's disease, Alzheimer's disease, and multiple sclerosis or stroke, (4) report being right-handed, (5) report being a native English speaker, and (6) obtain physician's approval that it was safe for them to participate in the study. Exclusion criteria included (1) conditions that would contraindicate an MRI scan, (2) failure to provide informed consent, (3) hospitalization within the past 6 months, (4) inability to walk 400 meters, and (5) significant cognitive-executive impairment, defined as a score on the Montreal Cognitive Assessment (MoCA) of <24.

2.2. Aerobic "Spin" Intervention Protocol. Consistent with our previous study [6], the group exercise intervention began with 20 minutes of Spin aerobic exercise three times a week for 12 weeks on stationary exercise cycles and was led by a qualified instructor. Importantly, the time of each session progressed based on the recommendation of the instructor by 1-2 minutes as needed to a maximum time of 45 minutes per session. Exercise intensity began at low levels [50% of maximal heart rate reserve (HRR)] and increased by 5% every week (if deemed necessary by the instructor) to a maximum of 75% maximal HRR.

The Spin intervention took place in a climate controlled fitness facility. The instructor guided the participants through a 5-minute warm-up and then a work out phase that included steady up-tempo cadences, sprints, and climbs. During the workout phase the target HRR reserve was maintained by averaging increases and decreases in intensity/HR. The goal was to maintain a 10% offset from the HRR goal during the workout phase. Thus, participants were within target HRR on average across the session. All participants wore HR monitors (FT7 Polar® Heart Rate monitor) and were instructed each day of their target HR range. Staff members also monitored and tracked the HR to ensure adequate intensity throughout each session. Weekly meetings in which each participant's HR was reviewed served as a way to encourage those with low attendance or HR to improve their performance for the next week.

2.3. Control Intervention Protocol. Participants in the control group were equalized (frequency and duration) to the Spin group for contact and monitoring. As such they reported the same facility with the same interventionist; however, instead of progressive aerobic exercise they engaged in group balance, stretching, and light muscle toning exercises. Similar to the aerobic group, the Balance intervention began with an initial 20-minute session steadily progressing to 45 minutes over the course of the 12-week intervention. Heart rate was consistently monitored to assess general intensity during each session.

2.4. Assessments. All assessments were done no more than 10 days before the start of or 10 days after the conclusion of the 12-week intervention period. Assessment sessions did not exceed two hours to alleviate participant fatigue.

2.5. Cardiovascular Fitness Assessment. To validate that the Spin exercise was effective at increasing cardiovascular fitness when compared to control, participants performed a YMCA

submaximal fitness test on a cycle ergometer. This submaximal test was used to estimate the participant's maximal oxygen uptake (VO_2max) prior to and after the intervention period. The selected submaximal test is much better tolerated than a maximum exertion treadmill test in the selected population (sedentary older adults). The YMCA test uses an extrapolation method in which heart rate workload values are obtained at 2–4 points during stages of increasing resistance and extrapolated to predict workload at the estimated maximum heart rate (e.g., 220-age). Estimated VO_2max is then calculated from the predicted maximum workload. Prior to beginning the test, the procedures were briefly explained and participants completed a 2-minute warm-up consisting of pedaling without load so that they could adapt to the ergometer for the first minute and then pedaling with a 0.5 kg·m load during the second minute. The YMCA submax test has an $R = 0.86$ with VO_2max and a SEE = 10% of the predicted VO_2max [15].

2.6. Cognitive Assessments. All participants completed a battery of neuropsychological tests to assess executive function and memory both before and after the interventions. The tests in the battery included the Controlled Oral Word Association (COWA) test (Letter and Semantic Fluency), the Hopkins Verbal Learning Test (HVLT), and forward and reverse digit span.

2.7. Scanning Protocol. During fMRI semantic verbal fluency acquisition, the participant's task was to overtly generate different exemplars of the respective category.

Similar to our previous work examining the neural underpinnings of semantic verbal fluency [14], a sparse temporal sampling approach was implemented to account for artifacts involved with overt speech. With a given repetition time (TR) (set at 5.83 seconds), image acquisition was delayed by 4 seconds during which participants were cued to make an overt response. Sagittal plane echo planar imaging was compressed into the final 1.83 seconds of each TR. Participants saw different categories (e.g., "flowers") at the center of a 1024 × 768 pixel video screen while being in the scanner and would generate a word describing an object they associate with that category (e.g., "rose"). This consisted of 8 blocked semantic verbal fluency conditions, followed by a control condition (reading the word "rest" aloud) that afforded contrast between semantic engagement and motor speech production. All responses were recorded including errors of commission (semantically unrelated responses or repeats) and omission (no response). Control blocks were jittered from 3–5 TRs per block and were presented after each semantic verbal fluency block. Each functional run in the scanner included 3 blocks requiring naming 8 objects in 6 different categories, with each participant completing 3 of these runs for a possible total of naming 144 objects. A total of 74 images were acquired per run with the first two images designated as equilibration images to be discarded.

Error analysis on scanner response proceeded as follows. Correct responses consisted of a semantically related member of the provided category (e.g., "lion" for ANIMAL category). Two raters scored the responses and inconsistencies were resolved by interrater agreement. Incorrect responses were semantically unrelated utterances (e.g., "ball" for ANIMAL), filler words (e.g., "um, er"), or no response given. Failure to respond comprised 80% of errors in the test sample.

Functional images were obtained on a 3T Siemens Trio (Erlangen, Germany) platform with a whole-brain, 1-shot gradient EPI scan using a 12-channel RF receive coil with the following parameters: 240 × 240 mm FOV, 64 × 64 matrix (3.75 × 3.75 mm in-plane resolution), TR = 5830 ms, time of acquisition (TA) = 1830 ms, echo time (TE) = 25 ms, and flip angle (FA) = 70°. Image voxels were isotropic using a 3.75 mm slice thickness (no gap) with 32 slices acquired per image. A high-resolution T1-weighted 3D rapid acquisition gradient echo (MP-RAGE) scan (TE = 4.13 ms, TR = 2000 ms; FOV = 240 mm; FA = 8°; matrix size = 256 × 192 mm, 128 × 1.3 mm sagittal slices) was obtained to provide anatomic reference. A laser position system was used to align the participants within the bore of the magnet. Head motion was minimized using foam padding and careful instructions were given to the participant about avoiding motion.

2.8. Data Analysis: Behavioral Data. Statistical analyses were conducted using Microsoft Excel and JMP 12 (SAS Institute, Cary, NC). Potential group differences at baseline on demographic and psychometric parameters were evaluated using a between-subjects t-test. To evaluate pre-post-differences between groups, change scores for behavioral data were computed using the convention: change = pre − post. Intervention effects were examined by independent sample t-test on change scores to determine between-group differences for the variables of interest: cognitive battery, cardiovascular fitness assessment, and in-scanner semantic verbal fluency performance.

2.9. Data Analysis: Imaging Data. For fMRI image processing, Analysis of Functional NeuroImages (AFNI) software and FMRIB Software Library (FSL) were used. Images were skull-stripped using a BASH shell optimized version of FSL Brain Extraction Tool (optiBET) [16]. After removal of equilibration images (first 2 TR) and linear trend removal, echo planar images were aligned to the first image of the initial EPI run using FSL's nonlinear registration tool (fNIRT). To minimize the effect of motion due to speaking artifact, we used an independent components analysis (ICA) approach as implemented by FSL's MELODIC and FIX suites. After slice timing correction and application of a 5 mm FWHM Gaussian kernel blur to account for spatial differences between subjects, we performed MELODIC's component identification on every run for each individual participant. We then used FSL's standard trained classifiers as implemented in their FIX suite with a component inclusion threshold of 18 components to regress out noise parameters. The selection of 18 components was performed after evaluation of 12, 15, 18, and 20 inclusion components with 18 having the optimal sensitivity and specificity. Image transform matrices to 2 mm MNI-152 space were computed using FSL for both

Table 1: Demographic and psychometric characteristics of participants at baseline.

	Spin group (n = 16, 10 females)	Balance group (n = 14, 6 females)
Age (years)	69.7 ± 6.34	72.09 ± 6.43
Education (years)	16.1 ± 2.77	15.46 ± 3.24
MOCA (maximum of 30)	28.21 ± 1.24	27.55 ± 1.12
Height (m)	1.68 ± 0.09	1.71 ± 0.11
Weight (kg)	93.15 ± 22.58	83.26 ± 12.34

MOCA: Montreal Cognitive Assessment; m: meters; kg: kilograms.

anatomic and echo planar imaging. After noise removal and image interpolation to standard space, we proceeded with a generalized linear model (GLM) regression approach evaluating semantic verbal fluency blocks against the control condition and baseline error term. AFNI's 3dDeconvolve program was used to calculate the GLM of activity against the control task (spoken word "rest"). A Block function was selected for the duration of the semantic verbal fluency block (8 TR) and regression coefficient beta weights were output for group analysis for each run.

To evaluate group differences as a result of the interventions, we performed a split-plot (2 between × 2 within) ANOVA as implemented in AFNI's 3dMVM [17] with intervention group as the between factor and timepoint (pre/post) as the within-subjects factor. 3dMVM tests allow groups with different n to be evaluated using a GLM. The specified generalized linear tests (GLT) afforded between and within group comparisons, as well as interaction effects while controlling for sphericity due to within-subjects comparisons. We used AFNI's 3dClustSim (compiled September 2015) program to correct for multiple comparisons with a voxel-wise threshold level $p < .01$ holding alpha at .01 for a minimum cluster size of 101 voxels at $2 \times 2 \times 2\,\text{mm}^3$ (MNI space). We selected this conservative threshold in light of recent work discussing random field theory in cluster correction [18]. We additionally added False Discovery Rate curves as a threshold check on the multivariate modeling results using 3dFDR in AFNI. The corresponding False Discovery Rate at the selected voxel threshold yields a $q \leq .02$ for all reported differences.

We additionally performed regression analyses using AFNI's 3dRegAna application to test for significant correlations between change scores in both semantic verbal fluency and change in estimated VO_2max in prediction of BOLD activity in the postsession. As above, statistical thresholds were set to $p < .01$, alpha = .02 with a minimum cluster size of 101 voxels in MNI space using 3dClustSim.

3. Results

One participant from each intervention group did not return for follow-up testing so the final cohort included 30 older adults (16 in Spin; 14 in Balance; $\boldsymbol{\mu} = 69.45 \pm 6.12$ years). The Spin and Balance group did not differ significantly at baseline in any characteristics (see Table 1).

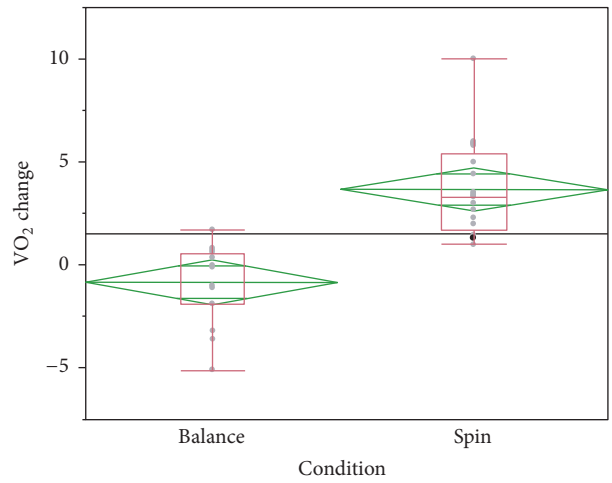


Figure 1: Difference in VO_2 change after 12-week intervention in quantile plots. Means are presented as center green lines. Group differences in VO_2 change are significant between the Spin and Balance groups ($p < .01$).

3.1. Behavioral Data. There was a significant difference between the change scores for the cardiovascular fitness assessment (estimated VO_2max) of the Spin group ($\boldsymbol{\mu} = 3.85 \pm 2.58$) and the Balance group ($\boldsymbol{\mu} = -0.05 \pm 1.05$); $t(29) = 4.63$, $p < .01$ (Figure 1). Participants did not show significant changes in biometric assessments (weight, basal heart rate, and blood pressure) in either group after interventions.

Cognitive Test Battery: A trend was shown for better performance in the Spin group after intervention on both semantic verbal fluency outside the scanner ($t(29) = 1.94$, $p = .06$) and the Hopkins Verbal Learning Test ($t(29) = 1.93$, $p = .06$). Group differences in postintervention comparisons were not significant for tests of forward digit span and reverse digit span.

In-scanner performance: in-scanner semantic verbal fluency performance improved after intervention in the Spin group as compared to the Balance control group ($t(29) = 2.6$, $p = .01$) (Figure 2). Error analysis between groups in postintervention assessment showed a significant change in error type. Errors of commission and omissions did not differ between groups in preintervention assessment ($t(29) = 1.2$, ns). However, during postintervention assessments, participants in the aerobic Spin training group showed fewer

Table 2: Results from AFNI 3dMVM analysis of group differences (aerobic versus Balance) in fMRI activity during a semantic fluency task at postsession scan. Data was thresholded for multiple comparisons using a voxel-wise cluster size of 101 voxels, $p < .02$ corrected. Cluster size is in voxels.

Region	X	Y	Z	Cluster size
Right cerebellum	−2.5	57.5	−51.5	2063
Right inferior temporal gyrus	−57.5	32.5	−21.5	1972
Right angular gyrus	−40.5	51.5	26.5	1660
Right superior orbital gyrus	−23.5	−59.5	−0.5	1333
Right superior temporal gyrus	−55.5	8.5	−6.5	467
Right precuneus	−9.5	71.5	51.5	371
Left middle cingulate cortex	9.5	26.5	41.5	353
Right middle temporal gyrus	−57.5	46.5	2.5	281
Right inferior frontal gyrus (*P. triangularis*)	−47.5	−46.5	−1.5	581

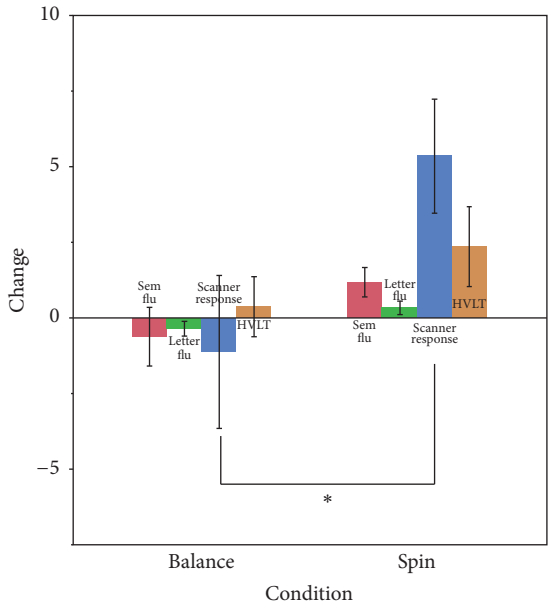


Figure 2: Group difference in the cognitive battery and in-scanner sematic fluency performance following the 12-week intervention. Sem Flu = semantic verbal fluency (outside scanner); letter flu = letter verbal fluency; scanner response = in-scanner semantic verbal fluency; HVLT = Hopkins Verbal Learning Test. ∗ denotes significant difference at $p = .05$.

errors of omission (no response) than the Balance group ($t(29) = 2.78$, $p < .01$).

3.2. Imaging Data. We performed a between-subjects t-test on presession regression coefficients to test if there were differences at baseline between the two participant groups. Negligible group differences were evident at the selected threshold in this comparison on whole-brain analysis. No differences were evident in language eloquent cortices.

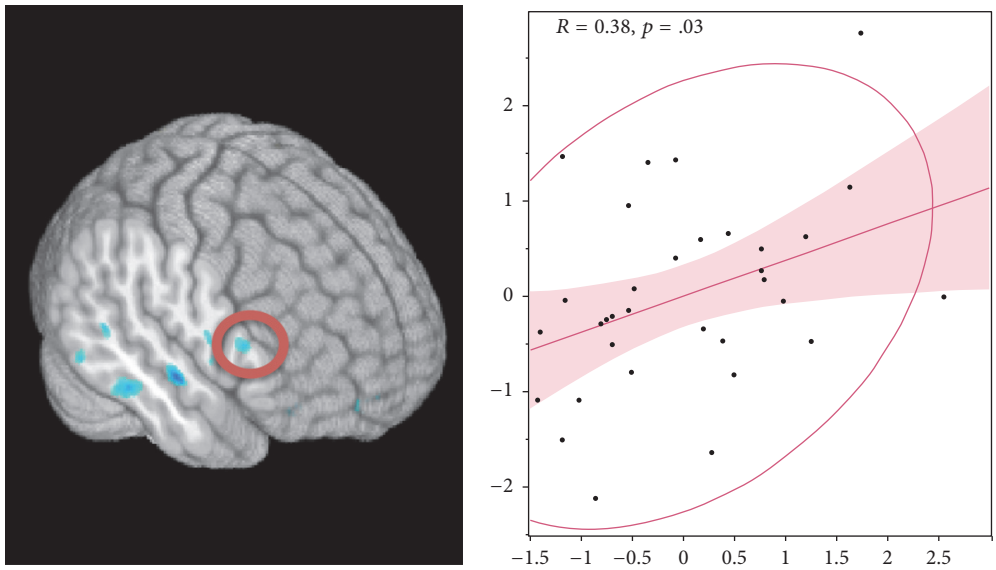
3.3. Postgroup Comparisons. Groups showed significant differences when comparing BOLD activity in postsession (see Table 2). Brain regions in the right hemisphere show significantly lower levels of BOLD activity in the Spin group. Importantly, decreased activity is shown in right hemisphere homologues of brain areas associated with semantic verbal fluency tasks including BA44/45, inferior temporal gyrus, and angular gyrus in the Spin group. Results of this analysis are shown in Figure 3 along with a correlation of change in VO_2 with right inferior frontal activity during fMRI. As shown in the figure, change in VO_2 was correlated with altered activity in right inferior frontal activity.

Results from regression analysis on VO_2 change data relating to postsession imaging results across participants are presented in Figure 4. As shown in the figure, increased VO_2 at postsession was correlated with decreased activity in right inferior frontal activity (indicated in blue) but increased left lateralized activity (indicated in orange).

Results from regression analysis of postsession semantic fluency performance within the scanner with fMRI activity are presented in Figure 5. As shown in blue, there was a negative correlation between improved semantic fluency and right lateral frontal activity. This indicates that improved semantic fluency was associated with decreased reliance on right lateralized structures.

4. Discussion

The goal of the present study was to examine changes in brain activity during a semantic verbal fluency task in a previously sedentary cohort of older adults following 12 weeks of aerobic Spin exercise when compared to a nonaerobic, Balance control group. Consistent with our hypothesis, participants completing the aerobic Spin exercise condition improved their cardiovascular fitness level and showed improved semantic verbal fluency performance during a category member generation within the MR scanner as compared to the Balance control group. Additionally, when comparing group imaging data in the postsession controlling for variance between groups in the presession, the aerobic Spin group showed less positive BOLD activity in right lateral frontal, right superior temporal, and right angular gyrus.



(a) (b)

Figure 3: (a) presents a 3D whole-brain rendering of group differences after 3dMVM analysis of post session imaging data between Balance and aerobic Spin group. Color intensity (blue hue) denotes significantly lower levels of activity in aerobic Spin group correcting for multiple comparisons with a voxel-wise threshold level $p < .01$ holding alpha at .01 for a minimum cluster size of 101 voxels. (b) presents a correlation of VO_2 change to change in inferior frontal activity after intervention. This indicates that the greater the VO_2 change, the larger the change in right frontal activity. Ordinate axis is VO_2 change and abscissa is change in frontal activity. All data is z-normalized.

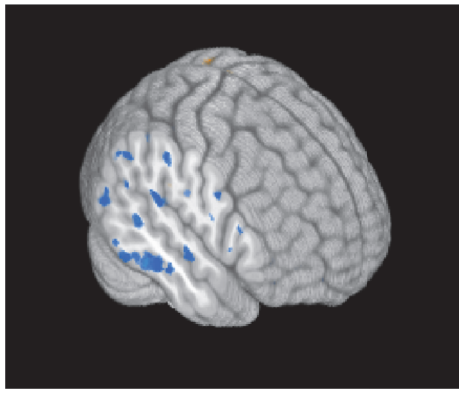


Figure 4: This figure presents a 3D whole-brain rendering of regression of VO_2 change data with fMRI activity across all participants. Particularly in right hemisphere, the greater the VO_2 change is in participants, the less likely they were to recruit right lateral frontal and right perisylvian language cortex. Orange color indicates increased fMRI activity with increased VO_2 and blue indicates decreased fMRI activity with increased VO_2. Data was corrected for multiple comparisons with a voxel-wise threshold level $p < .01$ holding alpha at 0.02.

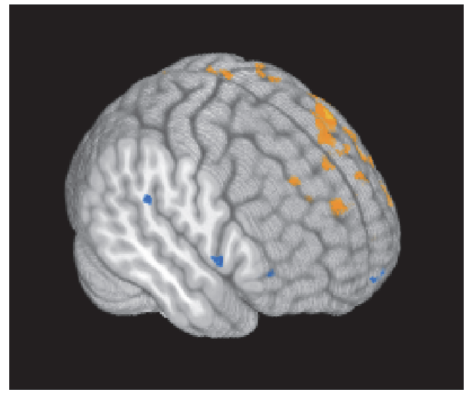


Figure 5: This figure presents a 3D whole-brain rendering of regression of in-scanner performance data with fMRI activity across all participants. A positive relationship was found between task performance and greater activity in left hemisphere (represented by orange). Activity in right language cortex was associated with decreased semantic fluency (represented in blue). Data was corrected for multiple comparisons with a voxel-wise threshold level $p < .01$ holding alpha at 0.02.

As expected, the older adults exhibited positive BOLD activity in the right frontal operculum during the preintervention fMRI. These findings corroborate our previous findings indicating higher bilateral positive BOLD in older adults while performing an fMRI semantic verbal fluency paradigm. This increased bilateral activity is indicative of worse performance when compared to individuals who evidenced more left lateralized inferior frontal activity [14, 19]. In the present study, when comparing right lateral frontal activity and semantic verbal fluency performance across all participants, participants showed a strong negative correlation between positive BOLD activity and semantic

verbal fluency output. That is, the more likely the individuals were to recruit right inferior frontal gyrus during semantic fluency, the worse their semantic verbal fluency output was. Importantly, the behavioral data are inline with and support the findings of a more efficient neural recruitment profile as measured by fMRI following the Spin intervention. To this point, the Spin group exhibited less BOLD activity after the intervention in right frontal regions while simultaneously demonstrating improvement in semantic verbal fluency output. Accordingly, the current findings suggest that an aerobic Spin intervention might facilitate a more efficient recruitment array during a semantic verbal fluency task. An intriguing finding in the current study is the difference in error types in semantic verbal fluency between groups evident after each intervention. Participants in the Spin aerobic exercise condition were less likely to make errors of omission after exercise than participants in the nonaerobic, Balance intervention. This may be associated with improved word finding within the semantic category selection task. Previous exercise interventions have also shown the efficacy of aerobic interventions in improving semantic verbal fluency [20, 21]. These findings support previous research indicating alterations in the neural recruitment profile, with a beneficial impact on executive performance following aerobic exercise [22, 23].

The finding of decreased activity in right inferior frontal regions being correlated with stronger semantic verbal fluency in older adults is, at face, seemingly at odds with a dominant model of hemispheric activity change respective of aging. The hemispheric asymmetry reduction in older adults (HAROLD) model has shown evidence that bilateral activity in older persons may be compensatory in nature [24]. This increased bilateral recruitment in older adults appears to be compensatory when considering generalized cognitive performance. However, we have shown that when task performance is compared with imaging data, increased bilateral recruitment tends to be detrimental to behavioral performance [10, 14]. This is consistent with findings from other laboratories that have reported increased error rates as associated with more bilateral recruitment in eloquent cortices [22, 25, 26]. However, as has been reported by numerous recent meta-analyses, it is extremely difficult to categorize bilateral BOLD activity as wholly compensatory or representative of inefficient processing [27, 28]. Among many numerous potential variables, in most aging-related imaging studies, physical activity is not included as a covariate. We interpret the current findings as potentially adding value to the debate on compensation or dedifferentiation in this respect. Much more work is needed to continue to explicate the complicated interrelationships of neural, vascular, and overall metabolic changes associated with aging that form the patterns of hemispheric activity changes so heavily modeled in the past few years.

The exact physiological mechanism responsible for the demonstrated changes in this exercise intervention study has yet to be determined. However, several candidates exist that need to be investigated to truly understand the mechanisms driving the changes evidenced in our exercise sample. Though beyond the scope of the present study, these mechanistic parameters may include, but are not limited to, an increase in brain-derived neurotrophic factor and other nerve growth factors [2, 8], changes in inhibitory systems function likely due to the neurotransmitter system gamma-aminobutyric acid ([29, 30]; see also [31]), and, most assuredly, increased vascular perfusion and optimized metabolic tone [32]. Strong evidence now exists showing that sedentary aging is associated with loss of cortical inhibition when compared with younger adults ([33–35] see [36] for recent review). Much of this literature has been informed by studies involving transcranial magnetic stimulation (TMS), but there is also growing evidence that cortical inhibition can be assessed using fMRI [30, 37] and that fMRI may be sensitive to aging-related changes in inhibition [14, 30, 37]. Aging-related changes in inhibitory function during language production, particularly in BA 44/45, have been reported with increasing frequency [19, 38, 39]. Future research should endeavor to incorporate multiple neuroimaging/neurophysiological techniques to better identify the physiological origin of the effect of exercise on verbal fluency.

An impressive finding of the current study is the relatively short amount of time (12 weeks) in which functional recruitment during a semantic verbal fluency task can be positively impacted by an exercise intervention. Baker et al. (2010) enrolled 33 participants with mild cognitive impairment over a 6-month span in which the participants engaged in 4 bouts of exercise per week. The participants followed a similar exertion schedule (though primarily treadmill-based) as the present study with heart rate targeted at 75–85% of HRR for the exercise sessions. After the 6-month training program semantic verbal fluency (measured by the DKEFS category fluency) significantly improved in females within the study cohort. Given this study was with patients diagnosed with mild cognitive impairment, the current findings may have clinical implications denoting the importance of beginning an aerobic exercise regimen prior to the onset of significant cognitive difficulties in older adults.

While Baker et al. (2010) did not use neuroimaging, numerous studies investigating the effects of aerobic exercise on executive functions have. In a seminal investigation, Colcombe et al. [40] demonstrated changes in activation patterns during a flanker task following 6-months of an exercise intervention. It should be noted, however, that the Colcombe study did not assess changes in the hemodynamic response at an earlier time point (e.g., 12 weeks); thus it is difficult to postulate when such changes might be observed. Additionally, the Colcombe study utilized a less intense (60–70% HRR) walking intervention, whereas we investigate a Spin exercise program designed to incorporate a higher intensity, interval-based workout (up to 75% of HRR with a 10% offset) within each session. Voelcker-Rehage et al. (2011) reported results on a 1-year walking intervention with previously sedentary older adults. This study ($n = 44$) reported improvements in executive function (visual search and flanker task) while showing reductions in recruitment of prefrontal regions during fMRI acquisition during

related tasks. The group interpreted the reduced activation as an increase in processing efficiency within the prefrontal regions. However, their exercise program was relatively low intensity (~60% HR peak within age group) and involved 30–45 minutes of walking for 12 months. With inflexible exercise targets respective of duration and HR intensity, it is possible that participants may have acquired peak effects earlier in the intervention and then maintained a plateau with respect to their aerobic performance. As such the current intervention is modeled as a progressive and adaptive protocol that may offer consistent performance gains throughout the duration of the exercise program.

There are notable limitations to the current work that should be addressed. Most immediately, the sample size is somewhat low in the present report. While this is problematic from a data extensibility standpoint, it also is exciting given the fact that we were able to detect changes in a small number of individuals (i.e., high power). Given this, however, additional work is clearly warranted to attempt to better characterize neural activity changes as a result of aerobic interventions. Secondly, the present study cannot easily characterize the nature of how the BOLD signal changes. As such, it is difficult to differentiate vascular effects from the intervention as compared to neural changes. While it is impossible to completely dissociate one from the other using the present modality, we must acknowledge that improvements in vascular flow dynamics as a result of increased physical activity may better characterize the BOLD changes shown in the present study. Again, future work is needed with alternate methodologies to identify the focal mechanism of change presented here. Finally, as a methodological note, pre/postassessments using MRI introduce sensitivity/specificity variation due to differences in MR field characteristics. We utilized B0 field maps to assess changes between sessions in MR scanner function. While these did not reveal a gross overall change, physiological characteristics of repeated scans could not be accounted for. Statistically, we attempted to compensate for sensitivity differences by using a consistent and reasonable threshold for functional activity.

In conclusion, the present study shows that a 12-week aerobic exercise intervention (Spin) alters brain activity in language networks and may be associated with the improvement in sematic verbal fluency. Additional work is warranted to further evaluate the effects of aerobic exercise on the neural substrates of language production in aging.

Disclosure

This work was presented as a Free Communication/Poster within the Physical Activity Interventions in Older Populations Wednesday, June 1, 2016, at the Annual Conference of the American College of Sports Medicine.

Competing Interests

The authors report no financial conflict of interests.

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Research Article

Fatigue and Muscle Strength Involving Walking Speed in Parkinson's Disease: Insights for Developing Rehabilitation Strategy for PD

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Background. Problems with gait in Parkinson's disease (PD) are a challenge in neurorehabilitation, partly because the mechanisms causing the walking disability are unclear. Weakness and fatigue, which may significantly influence gait, are commonly reported by patients with PD. Hence, the aim of this study was to investigate the association between weakness and fatigue and walking ability in patients with PD. *Methods*. We recruited 25 patients with idiopathic PD and 25 age-matched healthy adults. The maximum voluntary contraction (MVC), twitch force, and voluntary activation levels were measured before and after a knee fatigue exercise. General fatigue, central fatigue, and peripheral fatigue were quantified by exercise-induced changes in MVC, twitch force, and activation level. In addition, subjective fatigue was measured using the Multidimensional Fatigue Inventory (MFI) and Fatigue Severity Scale (FSS). *Results*. The patients with PD had lower activation levels, more central fatigue, and more subjective fatigue than the healthy controls. There were no significant differences in twitch force or peripheral fatigue index between the two groups. The reduction in walking speed was related to the loss of peripheral strength and PD itself. *Conclusion*. Fatigue and weakness of central origin were related to PD, while peripheral strength was important for walking ability. The results suggest that rehabilitation programs for PD should focus on improving both central and peripheral components of force.

1. Introduction

Gait disturbance significantly affects the quality of life in patients with Parkinson's disease (PD), particularly in the later stages. Due to the failure of current drug treatment for gait problems in patients with PD, neurorehabilitation programs are gaining popularity. However, such problems are also a big challenge for neurorehabilitation because the mechanisms causing the walking disability in PD are largely unknown. Fatigue and weakness are prominent symptoms in most PD patients, and both can affect the life quality and functional walking ability [1, 2]. Weakness of the lower extremities has been reported to be a risk factor for indoor falls in patients with PD [3]. Fatigue that occurs at the early stage and then progresses as the disease advances affects about half of the patients with idiopathic PD [2, 4], and PD-related weakness and fatigue have been linked to the severity and duration of PD, levodopa dose, activation

failure, and comorbidities such as depression and anxiety [4–6]. Chou and colleagues [7] reported that deep brain stimulation surgery did not change levels of PD-related fatigue. Understanding the mechanisms causing weakness and fatigue would be beneficial in developing suitable rehabilitation strategies for patients with PD.

Fatigue is a complicated disorder that has several domains, including physical fatigue, mental fatigue, reduced activity, and reduced motivation [8]. Recent studies have suggested that PD-related fatigue is both a nonmotor and a motor symptom [9, 10]. Fatigue in PD is commonly evaluated by questionnaire-based scales such as the Fatigue Severity Scale (FSS) [11] and Multidimensional Fatigue Inventory (MFI) [8, 12]. For example, Lou and colleagues found that PD patients suffered more fatigue than healthy controls in mental and physical domains using the MFI [12]. These questionnaire-based fatigue scales are convenient for screening fatigue; however they are subjective and cannot identify the cause or mechanism of fatigue.

The mechanisms of PD-related weakness and fatigue have yet to be clarified. Central nervous system- (CNS-) related factors (central fatigue) and peripheral factors (peripheral fatigue) may both contribute to weakness and fatigue [13]. It has been shown that fatigue in patients with CNS disorders such as multiple sclerosis involve both central and peripheral components. Central fatigue may include mental fatigue and a decrease in motivation [14, 15]. In contrast, peripheral fatigue may result from neuromuscular transmission failure along α motor neurons, neuromuscular junctions, muscle cell membranes, and factors within muscle fibers such as E-C coupling failure [16]. Recent studies have reported that the activation level (VA) of the maximum voluntary muscle contraction (VA) is lower in patients with PD than in age-matched controls [4, 17]. This suggests that PD patients are prone to have central fatigue; however this phenomenon has never been quantified.

In the laboratory, the total amount of fatigue can be quantified by the fatigue index, which is the ratio of maximum voluntary contraction (MVC) force before versus after fatigue-inducing exercise. Peripheral fatigue is commonly measured by the decrease in a muscle twitch force elicited by electrical stimulation of the peripheral nerve [18], while central fatigue is commonly quantified as the decrease in VA after fatigue-inducing exercise [13]. Quantifying the degree of central versus peripheral fatigue in PD patients is important for the development of suitable drug and rehabilitation interventions. Therefore, the aims of this study were to (1) investigate the level and mechanism of lower limb weakness and fatigue and (2) correlate the measured components to walking speed in patients with idiopathic PD.

2. Materials and Methods

2.1. Participants. The PD group included 25 patients (21 males, 4 females, mean age: 62.12 ± 10.23 years) with idiopathic PD recruited from the outpatient clinics at the Linkou Branch of Chang Gung Memorial Hospital in Taiwan (Table 1). Twenty-five healthy adults (8 males, 17 females, mean age: 59.04 ± 9.13 years) were recruited from the community as the healthy control (HC) group. The inclusion criteria for the PD group were (1) PD diagnosed according to the United Kingdom Brain Bank Criteria, (2) with Hoehn and Yahr stages II-III, (3) stable medication usage, and (4) Mini-Mental State Examination score ≥ 24. All PD patients were tested during a clinical "ON" status, with the more severe side being tested. The patients who had tremors when on medication or during recording and those with other central or peripheral neurological diseases or musculoskeletal injuries of the lower limbs were excluded from the study. Only the subjects with a sedentary lifestyle without regular exercise were recruited in both groups to avoid the confounding factor of physical activity level. Written informed consent was obtained from all subjects before participation. This study was approved by the Chang Gung Medical Foundation Institutional Review Board.

Table 1: Characteristics of the study subjects.

Group	PD (N = 25)	HC (N = 25)
Gender (female/male)	4/21	17/8
Age (years)	62.12 ± 10.23	59.04 ± 9.13
Height (cm)	167.04 ± 8.51	159.26 ± 8.89
Weight (kg)	68.44 ± 11.58	59.83 ± 11.17
Modified Hoehn and Yahr (HY) score, N		
HY = 1	6	—
HY = 1.5	5	—
HY = 2	6	—
HY = 2.5	4	—
HY = 3	4	—

2.2. Evaluation of Subjective Fatigue. Subjective fatigue was evaluated in all subjects using the FSS, a 9-item statement rating the severity of fatigue, and the MFI, a 20-item self-report instrument designed to measure fatigue. Both tools have been reported to have good validity and reliability [8], and both were carefully explained by an examiner who was blind to the purpose of this study.

2.3. Experimental Design. After a 30-minute rest, the force of MVC, VA level, twitch force, and fatigue indexes were evaluated. The subjects were seated on a custom-made knee extension force measurement system, which included a force transducer (AWU, Genisco Technology, CA, USA) coupled to a transducer amplifier (Gould Inc., Valley View, OH, USA), to measure the knee isometric extension force at 90 degrees of flexion [14]. Responses were sampled at 1000 Hz and recorded on a computer using a Power 1401 laboratory interface (Cambridge Electronic Design, Cambridge, UK) for offline analysis.

2.4. Maximum Voluntary Contraction (MVC). To record the MVC of the quadriceps muscle, each subject performed three

MVCs to warm up, followed by five MVCs which were recorded. The force trace was displayed on an oscilloscope (MetraByte AS 1600, Keithley Instruments, Inc., Cleveland, OH, USA) for real-time feedback. When performing MVC, the subjects were instructed to fully contract the quadriceps muscle for 5 seconds. Both verbal encouragement and visual feedback were given during the contraction. A rest period of 10 seconds was given between consecutive contractions. The amplitude of the MVC force was calculated from the force-time curve. To avoid possible changes in force contraction velocity before and after the fatigue-inducing exercise, the amplitude of MVC force was calculated by averaging the force level from the force peak until 0.5 s after the peak in each MVC.

2.5. Voluntary Activation Level (VA) Test and Twitch Forces. VA was measured using the interpolated twitch test [14, 19]. During the test, the quadriceps muscle was stimulated (Digitimer DS7A, Digitimer Ltd., Welwyn Court, UK) with surface electrodes. The pulse width of stimulation was 200 μs, and the stimulation intensity was supramaximal, that is, 120% of the intensity eliciting the maximum resting twitch. The supramaximal stimulus was delivered when the quadriceps was at rest and during MVC to elicit the resting twitch and the interpolated twitch ($T2$), respectively. The resting twitches were measured before and after MVC to obtain unpotentiated and potentiated resting twitches, respectively. Only the potentiated resting twitches were used ($T1$). The twitch forces were measured as the peak amplitude of the twitches, and VA was calculated using the following formula:

$$\text{VA} = \left(1 - \frac{T2}{T1}\right) \times 100\%. \quad (1)$$

The subjects then underwent the fatigue task, in which they were asked to repeat 5-second isometric MVCs of the quadriceps muscle, with 10-second rest periods in between, for 15 minutes. The subjects were encouraged verbally and visual feedback was provided to increase motivation during MVC. The MVC, VA, and twitch force were determined again after the fatigue task. Representative data for MVC, twitch force, and interpolated twitch force are shown in Figure 1(c).

2.6. Fatigue Indexes. The general fatigue index (GFI) was calculated as the ratio of postfatigue MVC to prefatigue MVC, and the central fatigue index (CFI) was calculated as the ratio of postfatigue VA to prefatigue VA. Central fatigue refers to a progressive decline in the ability to activate muscles voluntarily, and it has been attributed to impairment at sites of suprasegmental structures [13, 20]. By calculating the change in VA caused by exercise, exercise-induced central fatigue can be quantified. The peripheral fatigue index (PFI) was calculated as the ratio of the postfatigue twitch force to the prefatigue twitch force [14, 15]. The GFI, CFI, and PFI had values between 0 and 1, with a higher value indicating less general fatigue, central fatigue, and peripheral fatigue, respectively.

2.7. Walking Test. Functional ambulation ability was evaluated using a 6.5 m walking test. The subjects were asked to walk 6.5 m without assistance. To eliminate the influence of acceleration and deceleration, the average walking speed was measured over the middle 4.5 m.

2.8. Data Analysis. One-way ANOVA was used to analyze between-group differences in MVC, VA, twitch force, GFI, CFI, PFI, MFI, FSS, and walking speed (version 9.2, SAS Institute, Cary, NC, USA). Spearman correlation was used to analyze the correlations among levodopa equivalent dose (LED), UPDRS part III (motor part), and different components of fatigue. Stepwise regression analysis was used to identify the factors contributing to walking speed. The significance level was set at $p < 0.05$.

3. Results

All demographic and clinical data are shown in Table 1. There was no significant difference in age between the PD (62.12 ± 10.23 years) and HC (59.04 ± 9.13 years) groups ($p = 0.49$). The average LED of the patients was 258.92 ± 104.30 (range: 100–500) mg/day.

Figure 1 shows the representative force-time curves of MVC, twitch force, and interpolated twitch for one PD patient ((a)–(d)) and one healthy subject ((e)–(h)) before (pre) and after (post) fatigue tests. Between-group comparisons are shown in Figure 2. In the prefatigue state, VA was lower in the PD group (64.35 ± 17.37%) than in the HC group (74.65 ± 10.71%) ($F(1, 48) = 6.36$, $p = 0.02$; Figure 2(a)), suggesting that weakness originated from central fatigue in the PD group. There were no significant differences in MVC ($F(1, 48) = 0.07$, $p = 0.79$) or twitch force ($F(1, 48) = 2.64$, $p = 0.11$) (Figures 2(b) and 2(c)) between the two groups. The PD group had more subjective fatigue (MFI = 50.08 ± 14.80) than the control group (MFI = 38.52 ± 10.22) ($F(1, 48) = 10.33$, $p < 0.01$, Figure 2(d)), while no significant difference was found in FSS between the two groups (PD = 37 ± 13.28, control = 31.08 ± 12.67, $F(1, 48) = 2.6$, $p = 0.11$, Figure 2(e)). The PD patients had a slower walking speed (93.99 ± 34.6 cm/sec) than the HC group (122.17 ± 34.27 cm/sec) ($F(1, 47) = 10.93$, $p < 0.01$, Figure 2(f)). With regard to the fatigue indexes, fatigue-inducing exercise was associated with a significantly lower CFI in the PD group (79.48 ± 12.67) than in the HC group (88.53 ± 11.68) ($F(1, 48) = 6.9$, $p = 0.01$), suggesting that the PD patients experienced fatigue of central origin more easily than the healthy subjects (Figure 2(g)). No between-group difference was observed in PFI (PD: PFI = 81.13±15.71, HC PFI = 84.15 ± 13.37, $F(1, 48) = 0.54$, and $p = 0.47$), suggesting that both groups had similar levels of peripheral fatigue (Figure 2(h)). GFI was marginally lower in the PD group (74.22 ± 18.52) than in the HC group (84.37 ± 17.31%) ($F(1, 48) = 4$, $p = 0.05$, Figure 2(i)).

We further performed correlation analysis between measures (Table 2). Pearson correlation coefficients showed that MVC correlated with both VA ($r = 0.56$, $p < 0.001$) and resting twitch ($r = 0.74$, $p < 0.001$) in the PD group, whereas

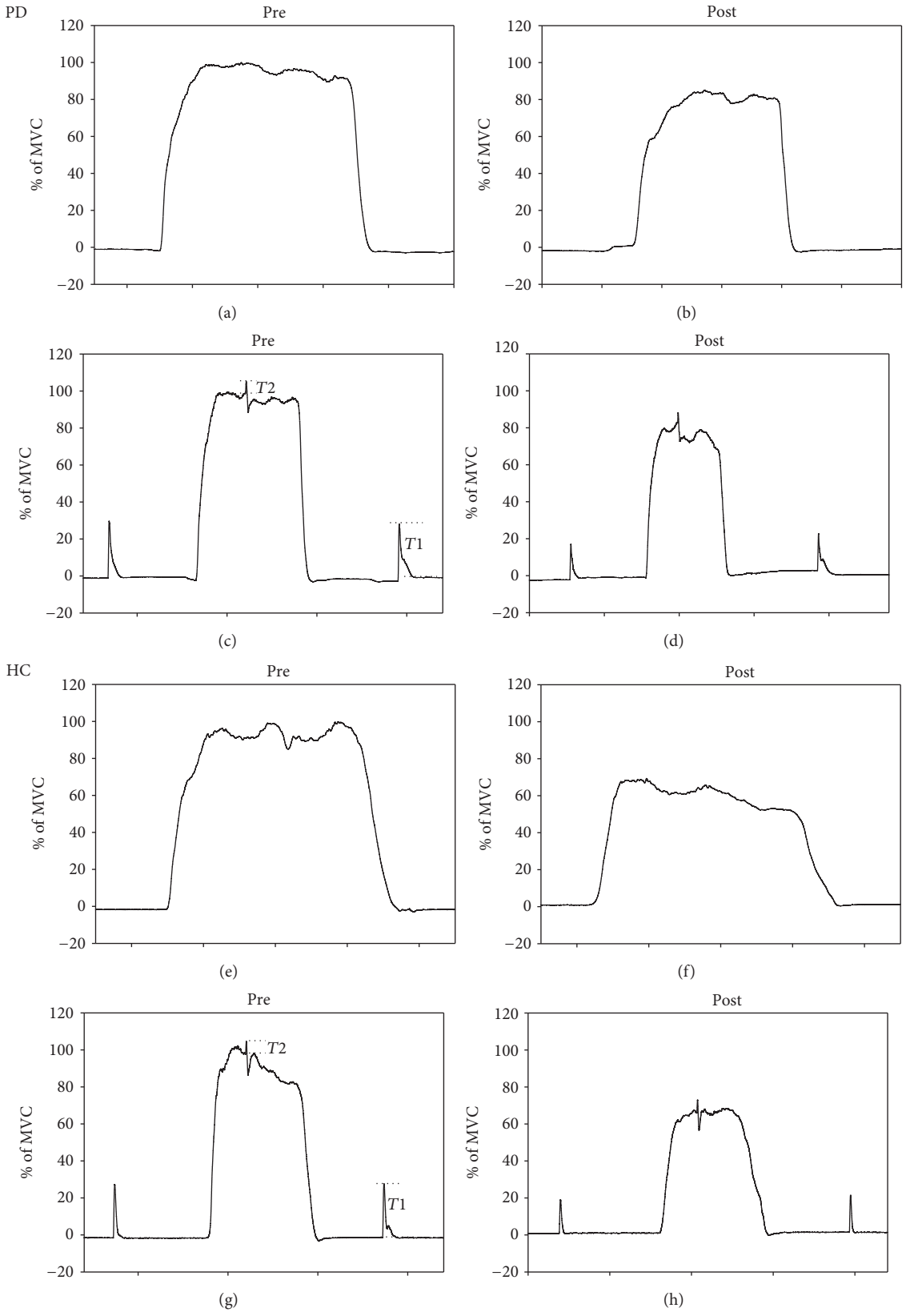

Figure 1: Representative force-time curves of MVC, twitch force, and interpolated twitch for one PD patient ((a)–(d)) and one healthy subject ((e)–(h)) before (pre) and after (post) fatigue. The y-axis shows the percentage of the peak MVC, with the prefatigue maximum set to 100%. T_1: potentiated twitch was also used to represent twitch force.

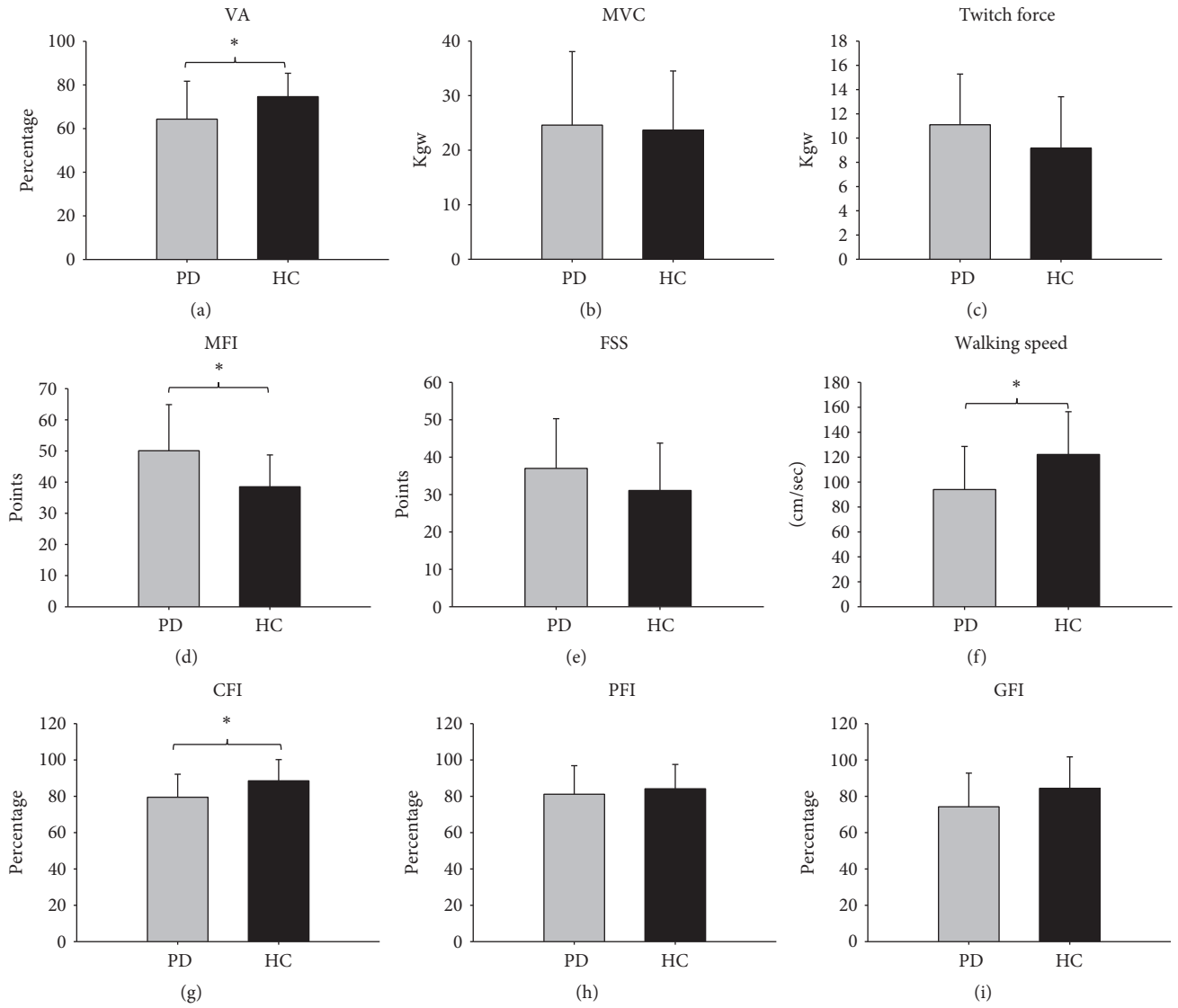

Figure 2: Differences between the PD and HC groups in (a) VA, (b) MVC, (c) twitch force, (d) MFI, (e) FSS, (f) walking speed test, exercise-induced (g) central fatigue, (h) peripheral fatigue, and (i) general fatigue indexes in the PD and HC groups. $^{*}p < 0.05$.

it correlated only with twitch force ($r = 0.71$, $p < 0.001$) in the HC group. No significant correlations were found between MFI and objective fatigue parameters including GFI (PD: $p = 0.27$, HC: $p = 0.92$), CFI (PD: $p = 0.25$, HC: $p = 0.42$), or PFI (PD: $p = 0.52$, HC: $p = 0.76$). Stepwise regression analysis revealed that walking speed could be affected by having PD itself and by twitch force (R-square = 0.23, $p < 0.01$).

The spearman correlation analysis showed that LED and VA correlated with the UPDRS III score ($r = -0.63$, $p = 0.022$ and $r = -0.65$, $p = 0.025$, resp.), but not with other parts. Moreover, we did not find any correlations between LED and different types of fatigue (GFI: $r = 0.12$, $p = 0.57$; CFI: $r = 0.25$, $p = 0.22$; and PFI: $r = 0.20$, $p = 0.34$) and/or between UPRDS UPDRS III and different types of fatigue (GFI: $r = 0.10$, $p = 0.75$; CFI: $r = -0.41$, $p = 0.16$; and PFI: $r = 0.03$, $p = 0.92$).

4. Discussion

The current study revealed that PD patients had lower VA, lower CFI, and more subjective fatigue than the HCs. The MVC of the PD group correlated with both VA and twitch force, whereas the MVC of the control group correlated only with the twitch force. The slower walking speed in the PD patients could be explained by both having the disease of PD and loss of twitch forces.

The finding of a lower VA in the patients with PD is consistent with previous studies [4, 17]. VA reflects the ability of the CNS to drive the muscular system without being confounded by peripheral muscle strength [19]. A lower VA suggests that PD patients have subclinical weakness of central origin. The lack of a significant difference in twitch force between the PD and HC groups further confirms that

Table 2: Correlation analysis between variables in the two groups.

Correlation	PD						HC					
	MFI		MVC		Speed		MFI		MVC		Speed	
	r	p	r	p	r	p	r	p	r	p	r	p
CFI	−0.24	0.25					0.17	0.42				
GFI	−0.23	0.27					−0.02	0.92				
PFI	−0.13	0.52					−0.06	0.76				
VA			0.56	<0.01*	−0.07	0.73			0.38	0.06	0	0.99
TW			0.74	<0.01*	0.28	0.19			0.71	<0.01*	0.18	0.40
MVC					0.16	0.45					−0.14	0.51

PD, Parkinson's disease; HC, healthy control; MFI, Multidimensional Fatigue Inventory; CFI, central fatigue index; PFI, peripheral fatigue index; GFI, general fatigue index; VA, activation level; TW, twitch force; MVC, maximum voluntary contraction.
*Significant correlation, $p < .05$.

a peripheral mechanism may not be involved. In terms of fatigue, the PD patients had a lower CFI than the HCs, suggesting that the PD patients had more fatigue of central origin after exercise. Quantification of exercise-induced fatigue has seldom been studied in PD. Although a lower activation level and higher general fatigue have been reported [4, 17], central and peripheral exercise-induced fatigue have never been investigated separately in patients with PD. To the best of our knowledge, this is the first study to identify exercise-induced central and peripheral fatigue in PD patients using a well-established laboratory technique that has been used in other neurological diseases such as multiple sclerosis [14]. Stevens-Lapsley et al. reported that general fatigue in the quadriceps muscle was only greater in PD patients with a low motor score but not in those with a high motor score compared to controls [4]. This is consistent with our results which revealed only a marginally lower GFI in the PD patients. Together with the finding of no difference in PFI between the PD and HC groups, the current study confirms that fatigue in PD is of central origin and that only the CFI is sensitive enough to detect such fatigue.

In this study, the PD group had more exercise-induced central fatigue and reported a higher MFI compared to the HC group. However, no significant correlation was identified between the MFI and CFI. The scale of the MFI, a self-reported psychometric measurement instrument, is not linear [8], and this nonlinearity is probably the cause of the poor correlation with the CFI.

The MVC in the PD group was significantly correlated with both the forces of central (VA) and peripheral (resting twitch) origin, whereas the MVC in the HC group was only correlated with the force of peripheral origin. In addition, there was no difference in the twitch force between the two groups. It is generally accepted that age-related weakness is a result of peripheral muscle weakness rather than reduced neural drive. A study on the force of the quadriceps muscle reported an approximately 50% lower twitch force but no change in either mean motor unit firing rates or activation level in older compared to younger subjects [21]. The possible factors contributing to peripheral weakness include a reduction in dietary protein, humoral effects of gonadal steroids, increases in catabolic stimuli, and decreased levels of physical activity [22]. The correlation between MCV and VA in the PD patients and the similar twitch force between the PD and HC groups suggest that, in addition to peripheral weakness seen in the elderly, PD patients suffer from weakness of central origin.

No significant difference in MVC or GFI (calculated from the change in MVC) was found between the PD and HC groups, suggesting that MVC alone is not sensitive enough to identify PD-related weakness. MVC measures both the central and peripheral components of fatigue [19, 23], and it is possible that a significant change in the central component, for example, lower VA, in the patients with PD contributed much less than the peripheral component resulting in similar changes in the PD and HC groups to MVC. On the other hand, the lower VA could be compensated by the increase in variability of firing rate of single motor units in PD [24]. According to the force-frequency relationship, the MVC force could be influenced by motor unit firing characteristics even with all the motor units fully recruited by the CNS [25].

The underlying mechanisms of PD-related activation failure and central fatigue are complicated. Central fatigue represents a failure of physical and mental tasks that require self-motivation and internal cues in the absence of demonstrable cognitive failure or motor weakness. Serotonin and dopamine have been identified as critical neurotransmitters in fatigue [26]. An animal study showed that levels of extracellular dopamine and 5-HT neurotransmitters increased significantly during exhausting exercise [27]. A reduced level of dopamine has also been reported in fatigued rats [28]. The reuptake of dopamine, but not the regulation of serotonin levels, has been reported to restore performance to some extent and in particular heat-mediated central fatigue [28, 29]. Pharmacological evidence further supports the importance of dopamine in fatigue [28]. In addition to dopamine deficiency, several lines of evidence suggest that the serotonergic system is also involved in the pathophysiology of PD [30, 31]. The failure of activation and central fatigue in PD patients is likely due to aberrant dopamine and serotonin systems. The potential mechanism may be related to dopamine transporter binding in the posterior putamen, the functional organization of basal ganglia, and connections of the basal ganglia to cortical motor and premotor areas

[6]. Basal ganglia are involved in the limbic modification of cortical motor output via the dopaminergic system and the serotonin pathway [32]. Such limbic modification could affect motivation, thereby influencing the ability to sustain voluntary activation after exercise. However, we failed to find a correlation between LED or UPDRS III and fatigue measures. This is perhaps not surprising, because the experiments were performed when the patients were still taking medications, and medications are likely to help partially compensate for fatigue. Further studies including patients not taking medications are warranted to evaluate the correlation between daily levodopa supplements and serotonin-related factors such as depression and fatigue measures.

Other mechanisms also contribute to central fatigue. For example, central fatigue may result from insufficient drive from supraspinal sites [13, 20] because of a lack of subject motivation [32]. Recent studies have shown that during exhaustive exercise, group III/IV muscle afferents inhibit the motor cortex and promote central fatigue [33, 34]. During exercise, inadequate oxygen delivery to the brain may contribute to the development of fatigue [28, 35]. Future studies should focus on whether PD patients are more sensitive to group III/V inhibition and more vulnerable to inadequate brain oxygen delivery.

We also found a reduced walking speed in the PD patients, with an average of 93.99 ± 34.6 m/s in the PD group compared to 122.17 ± 34.27 m/s in the HC group, consistent with the study by Yang et al. [33]. Furthermore, we found that this reduction in walking speed could be partially explained by the peripheral component of knee extensor force. Although the correlation was not enough to infer their causal relationship, this finding is compatible with a previous study which demonstrated that muscle power was a significant determinant of walking speed in patients with PD even after adjusting for UPDRS motor score [34]. Therefore, improvements in peripheral muscular strength may help to improve the walking ability of PD patients. However, it should be noted that several other factors such as postural abnormalities, shorter stride, smaller forward moment velocity, and abnormal trunk muscle strength may also slow the walking speed in patients with PD [33].

4.1. Limitations. Tremors that may potentiate resting twitch force may have been a confounding factor in this study. However, we excluded subjects with obvious tremors and those with tremors during recording to avoid this issue. Moreover, only potentiated twitches recorded during muscle activation were analyzed. Thus, the influence of tremors was minimized by the experimental design. Another potential limitation is that we did not balance the gender distribution in the two groups. The reported influence of gender on fatigue has been inconsistent, and a gender difference has been reported in muscles of the upper extremities [35], but not of the lower extremities [35, 36]. In the present study, muscles in the lower extremities, that is, the quadriceps muscles, were evaluated and no difference in the GFI of knee extensor was found between groups. Hence, the difference in gender distribution is unlikely to have influenced the results.

5. Conclusion

In this study, we found that PD patients suffered from weakness of central origin in the prefatigue state. The patients reported more subjective fatigue and presented with more exercise-induced central fatigue than the HCs. In addition, peripheral strength was found to be an important factor with regard to the walking ability of the patients with PD. These results provide an insight into the mechanism of weakness and gait problems and may help with the development of rehabilitation programs for patients with PD in improving activation level, overcoming central fatigue and subjective fatigue, which will in turn be helpful to overcome PD-related weakness and fatigue. Peripheral muscle strength should be enhanced to improve walking speed.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contributions

This study was designed by Ying-Zu Huang and Ya-Ju Chang. The experiments were carried out by Fang-Yu Chang and Wei-Chia Liu with the help of Ying-Zu Huang, Ya-Ju Chang, and Li-Ling Chuang. All authors contributed to the interpretation of the results, prepared the draft and critically reviewed the manuscript for intellectual content, and agreed on the final version of manuscript.

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Research Article

Brain White Matter Impairment in Patients with Spinal Cord Injury

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It remains unknown whether spinal cord injury (SCI) could indirectly impair or reshape the white matter (WM) of human brain and whether these changes are correlated with injury severity, duration, or clinical performance. We choose tract-based spatial statistics (TBSS) to investigate the possible changes in whole-brain white matter integrity and their associations with clinical variables in fifteen patients with SCI. Compared with the healthy controls, the patients exhibited significant decreases in WM fractional anisotropy (FA) in the left angular gyrus (AG), right cerebellum (CB), left precentral gyrus (PreCG), left lateral occipital region (LOC), left superior longitudinal fasciculus (SLF), left supramarginal gyrus (SMG), and left postcentral gyrus (PostCG) ($p < 0.01$, TFCE corrected). No significant differences were found in all diffusion indices between the complete and incomplete SCI. However, significantly negative correlation was shown between the increased radial diffusivity (RD) of left AG and total motor scores (uncorrected $p < 0.05$). Our findings provide evidence that SCI can cause not only direct degeneration but also transneuronal degeneration of brain WM, and these changes may be irrespective of the injury severity. The affection of left AG on rehabilitation therapies need to be further researched in the future.

1. Introduction

Previous studies on animals and humans have observed brain cortical reorganization following spinal cord injury (SCI). For example, animal models have demonstrated significant anatomical atrophies in the sensorimotor areas following SCI [1–5]. In human studies, some scholars have researched the cortical changes following SCI using voxel-based morphometry (VBM) [6, 7]. Cortical reorganization has been considered an obstacle to sensorimotor function recovery following SCI [8]. Notably, most previous studies have focused on the cortical changes within the SCI [7–13], and the possible changes in white matter (WM) integrity in the brain following SCI have not been fully clarified.

Because the spinal cord contains large numbers of ascending and descending fibres that are directly or indirectly connected to the nuclei and cortices of the brain, SCI will completely or partially destroy these fibre tracts at the injury level. However, it remains unknown whether SCI could indirectly impair or reshape the WM of human brain and whether these changes are correlated with injury severity, duration, or clinical performance. Clarifying these questions will aid the understanding of the mechanisms underlying WM changes in the brain following SCI and possibly contribute to the development of new rehabilitation therapies in the future, including transcranial magnetic stimulation [14–16] and gene chip implantation [17]. To our knowledge, only a few structural studies have explored SCI-related WM changes [8, 18–20]. However, these studies did not clarify whether the changes in the brain WM integrity correlated with injury severity, duration, or clinical performance. Diffusion tensor imaging (DTI) provides unique noninvasive

Table 1: Clinical data for the spinal cord injured individuals.

ID	Age [yrs]	Gender	Etiology of the injury	Time since injury [yrs]	Level of lesion*	Side of the injury	ASIA*	Motor (0–100)	Sensory* (0–224)	VAS
1	55	F	Stab wound	0.75	C3-4	Left	D	89	113	6
2	50	M	Hit by weights	1	C5–7	Bilateral	A	24	80	10
3	34	F	Vehicle accident	1	L1	Bilateral	D	74	190	4
4	38	M	Hit by weights	0.08	T12	Bilateral	A	50	157	4
5	28	F	Fall injury	0.58	L1	Bilateral	D	70	160	0
6	51	M	Vehicle accident	1.33	L1	Bilateral	A	50	84	10
7	55	M	Hit by weights	9	L3	Bilateral	A	50	144	9
8	42	M	Hit by weights	9	T12	Bilateral	A	56	160	9
9	38	M	Hit by weights	7	T12	Bilateral	A	56	144	9
10	40	F	Injury by conveyor	12	L1-2	Bilateral	D	96	148	8
11	66	F	Stab wound	0.17	T8	Bilateral	C	80	172	0
12	52	M	Stab wound	0.25	T10	Bilateral	A	50	168	0
13	60	M	Vehicle accident	3	C3–7	Right	C	70	204	9
14	33	M	Fall injury	0.1	L1	Bilateral	B	62	224	0
15	56	M	Injury by collapse	33	C4	Bilateral	A	60	158	9

*The level of lesion refers to the neurological level. *ASIA impairment scale: A, complete, no sensory or motor function is preserved in sacral segments S4-S5; B, incomplete, sensory but not motor function is preserved below the neurological level and extends through sacral segments S4-S5; C, incomplete, motor function is preserved below the neurological level, and more than half of the key muscles below the neurological level have a muscle grade of <3; D, incomplete, motor function is preserved below the neurological level, and at least half of the key muscles below the neurological level have a muscle grade of >3. *Sensory score: sum of segmental light touch and pinprick classifications. ASIA: American Spinal Injury Association. VAS: visual analogue scale.

insights into the structural connectivity of the living brain that can help us investigate the microstructure and WM integrity [21]. In the present study, we used tract-based spatial statistics (TBSS) to investigate regional changes in WM integrity after chronic SCI. TBSS is a voxel-wise data-driven method that quantifies the diffusion indices at the centre of the WM tracts (i.e., WM skeleton), which dramatically diminishes the registration problems of diffusion indices, and does not need smoothing before statistics and thus can improve the accuracy and interpretability of group-wise statistics [22]. We hypothesized that WM changes in the brain following SCI would be found in the sensorimotor system. Additionally, we are also interested in the impact of the severity of SCI (i.e., complete SCI (CSCI) versus incomplete SCI (ISCI)) on the integrity of remote brain WM and the correlations between WM fibre tract changes and clinical variables.

2. Materials and Methods

2.1. Subjects. Fifteen right-handed patients with SCI (10 male and 5 female patients, with a mean age of 46.5 ± 11.2 years and an age range of 28–66 years) were enrolled in this study. Eight patients were labelled grade A, and seven were labelled grades B to D according to the American Spinal Injury Association (ASIA) Impairment Scale 2012 (http://asia-spinalinjury.org). The courses of the diseases ranged from one month to thirty-three years, with a mean of 5.2 ± 8.7 years. All patients had no brain lesions that were confirmed by conventional MRI, and they had never (previously or at present) suffered from traumatic brain injury related symptoms such as loss of consciousness, headache, dizziness, memory loss, attention deficit, depression, or anxiety. All of the patients suffered from bilateral sensorimotor dysfunction, with the exceptions of two patients who exhibited only right- or left-side dysfunction. All of the patients underwent a comprehensive clinical assessment prior to the MR scan; this assessment included a sensory score and motor score that were assessed by a qualified clinician using the ASIA classification scale [23, 24] and visual analogue scale (VAS). The sensory levels were assessed by testing two aspects of sensation, that is, light touch and pinprick sensation (sharp-dull discrimination), at key points in each dermatome (C4–S4-5, bilateral). The motor function assessment involved testing the functions of key muscles in areas corresponding to 10 paired myotomes (C5–T1 and L2–S1). Fifteen age-, gender-, and years of education-matched right-handed healthy volunteers (10 male and 5 female controls with a mean age of 45.0 ± 10.6 years and a range of 26–65 years) were recruited as NCs. Table 1 provides detailed information about the SCI patients.

The methods were carried out in "accordance" with the approved guidelines, including any relevant details. This study protocol was approved by the Ethics Committee of Xuanwu Hospital, Capital Medical University, Beijing, China. Written informed consent was obtained from each participant in accordance with the Declaration of Helsinki.

2.2. Magnetic Resonance Imaging (MRI) Acquisition. All participants were scanned on a 3.0 T Magneton Trio Tim MRI scanner (Siemens Healthcare, Forchheim, Germany).

Table 2: White matter regions showing significantly decreased fractional anisotropy in SCI patients.

White matter regions	Peak MNI coordinates			Cluster size (voxels)	Peak p value
	X	Y	Z		
L angular gyrus	−35	−61	34	50	0.002
R cerebellar	23	−70	−33	57	0.002
L precentral white matter	−7	−22	55	65	0.002
L lateral occipital	−32	−83	14	107	0.001
L superior longitudinal fasciculus	−33	−62	26	114	0.002
L supramarginal gyrus	−40	−47	33	129	0.005
L postcentral white matter	−11	−34	58	145	0.002

Conventional brain axial fluid-attenuated inverse recovery (FLAIR) and magnetization-prepared rapid acquisition gradient-echo (MPRAGE) sequences (voxel size 1.0 × 1.0 × 1.0 mm) were acquired prior to the DTI scan to exclude abnormal brains. The DTI experiments were performed using a single-shot gradient-echo echo-planar imaging sequence with the following imaging parameters: TR = 9500 ms, TE = 90 ms, NEX = 1, matrix = 128 × 128, FOV = 256 × 256 mm^2, nonzero b value = 1000 s/mm^2, gradient directions = 64, slice thickness = 2 mm, and slice gap = 0. A total of 64 contiguous slices parallel to the anterior commissure-posterior commissure line were acquired.

2.3. Data Processing and Diffusion Tensor Imaging (DTI). Postprocessing was performed using TBSS implemented using the FSL 5.0.1 software package (Centre for FMRIB, Oxford University, Oxford, UK; https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) [22]. The following postprocessing steps were included: all DTI images were visually checked by two experienced radiologists to eliminate images with apparent artefacts caused by, for example, head motion, susceptibility artefacts, or instrument malfunction; eddy current corrections were applied, and motion artefacts were removed using affine alignment. Next, the nonbrain tissues were removed using the brain extract tool (BET), which not only reduces the computation times of the DTI fitting and tracking processes but also improves the accuracy of the spatial registration. The diffusion tensor of each voxel was then fit using a linear least squares algorithm, and the fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) maps were calculated based on the eigenvalues of diffusion tensors [25]. For the TBSS analysis, the main procedures were as follows: the entire FA dataset was nonlinearly coregistered to the Montreal Neurological Institute (MNI) FA template in the FSL database. Next, a mean FA skeleton from the mean FA images of all of the subjects was derived and represented the centre of the white matter tracts common to the group. An FA threshold of 0.25 [26] was used to involve only the major white matter pathways while eliminating peripheral tracts that are susceptible to misregistration. Finally, each aligned FA map was then projected back onto the skeleton to generate a subject-specific FA skeleton. The processes of nonlinear warping and skeleton projection of the FA maps were also applied to MD, AD, and RD maps.

2.4. Statistical Analysis. TBSS using a nonparametric permutation test (5,000 permutations) was performed to compare the FA differences between the SCI patients and the NCs. The permutation test was performed with a fixed-effect general linear model (GLM) with the age and gender as nuisance covariates. Statistical significance was set at $p < 0.01$ and corrected for multiple comparisons using the threshold-free cluster enhancement (TFCE) method. Next, the regions that exhibited alterations in the FA due to SCI were defined as the regions of interest (ROIs), and the mean FA, MD, RD, and AD values of each ROI of each subject were extracted. Two-sample t-tests were used to compare the differences in these diffusion indices between the SCI and NC subjects and between the CSCI and ISCI patients ($q < 0.05$, false discovery ratio- [FDR-] corrected) after controlling for age and gender effects. Finally, partial correlation analysis was performed to explore the associations of the clinical variables with the diffusion indices in SCI group, with age and gender serving as nuisance covariates ($p < 0.05$, uncorrected).

3. Results

3.1. Brain WM Abnormalities in the SCI Patients. Compared to the normal controls (NCs), significantly lower fractional anisotropy (FA) values were observed in the left angular gyrus (AG), right cerebellum (CB), left precentral gyrus (PreCG), left lateral occipital region (LOC), left superior longitudinal fasciculus (SLF), left supramarginal gyrus (SMG), and left postcentral gyrus (PostCG) in SCI patients ($p < 0.01$, TFCE corrected) (Table 2 and Figure 1).

ROI-wise comparisons generally revealed decreases in the FA and increases in the radial diffusivity (RD) of these brain regions. Significant increases in mean diffusivity (MD) were identified in the right CB, left LOC, and left SLF. In contrast, no significant differences in axial diffusivity (AD) between the SCI patients and NCs were found

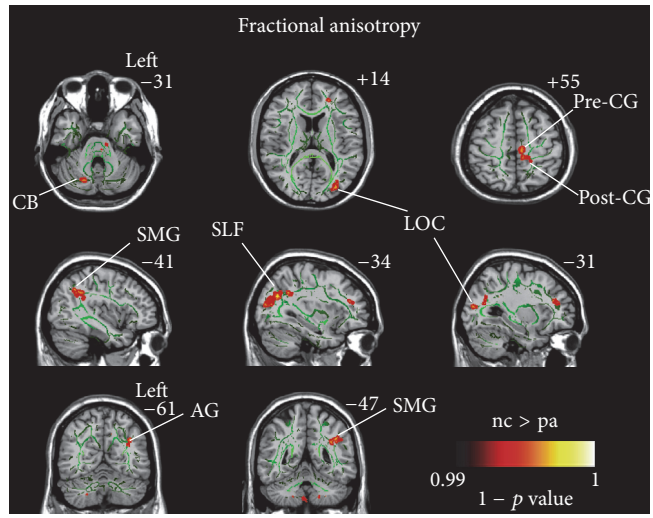

Figure 1: Differences in fractional anisotropy (FA) between the SCI patients and healthy controls based on tract-based spatial statistics (TBSS) ($p < 0.01$, corrected using threshold-free cluster enhancement). Hot color represents $1 - p$ values. It is overlaid on the gyrus skeleton (green) and the MNI 152 template. Significant decreases in FA following SCI occurred in the left angular gyrus (AG), right cerebellar (CB), left precentral gyrus (PreCG), left lateral occipital region (LOC), left superior longitudinal fasciculus (SLF), left supramarginal gyrus (SMG), and left postcentral gyrus (PostCG).

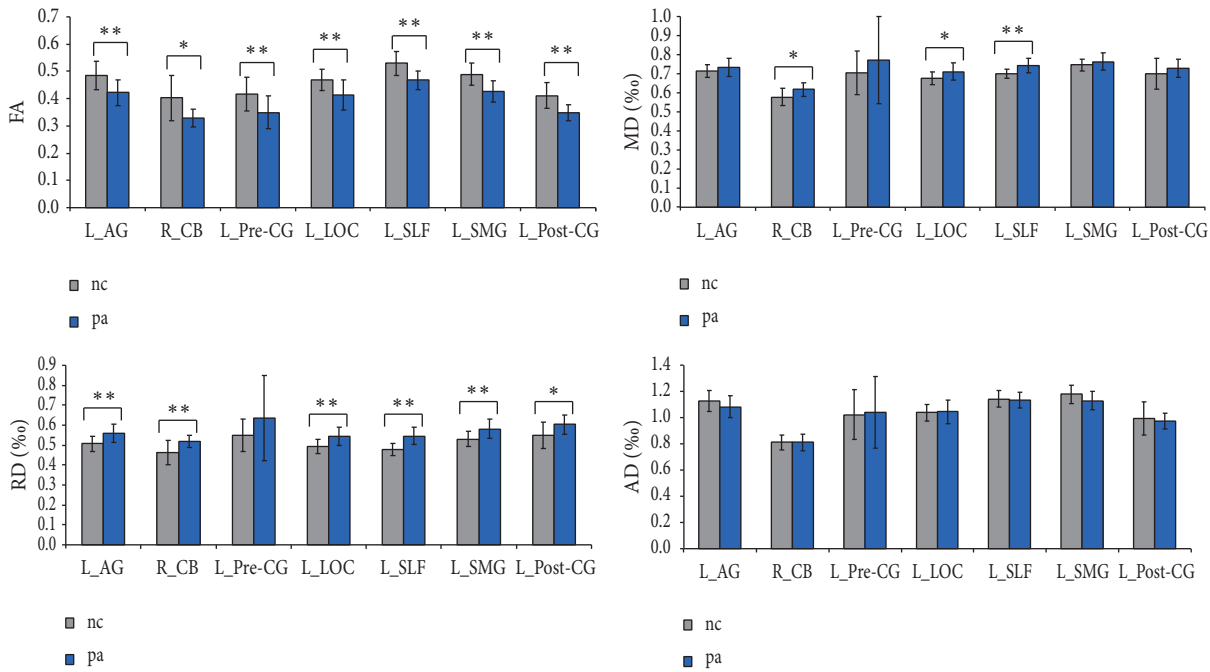

Figure 2: Differences in diffusion metrics between the SCI patients and healthy controls based on region of interest (ROI) analysis. The ROIs were extracted based on the findings of TBSS. ∗∗ represents statistical significance with FDR $q < 0.05$; ∗ represents statistical significance with unadjusted $p < 0.05$. The error bar indicated standard deviation (SD). AG: angular gyrus, PreCG: precentral gyrus, LOC: lateral occipital region, SLF: superior longitudinal fasciculus, SMG: supramarginal gyrus, PostCG: postcentral gyrus, CB: cerebellar, FA: fractional anisotropy, MD: mean diffusivity, RD: radial diffusivity, AD: axial diffusivity.

($q < 0.05$, corrected using FDR or uncorrected $p < 0.05$; Figure 2). To account for any influence of injury sides on our data, we further investigated the WM changes in SCI patients with bilateral injuries (unilateral injured patients excluded) and observed similar patterns of changes as before (Figure S1, in Supplementary Material available online at https://doi.org/10.1155/2017/4671607), which may suggest that the sides of SCI had little influence on the WM changes in brain. However, because of the relatively small sample size, we cannot directly compare the influence of sides

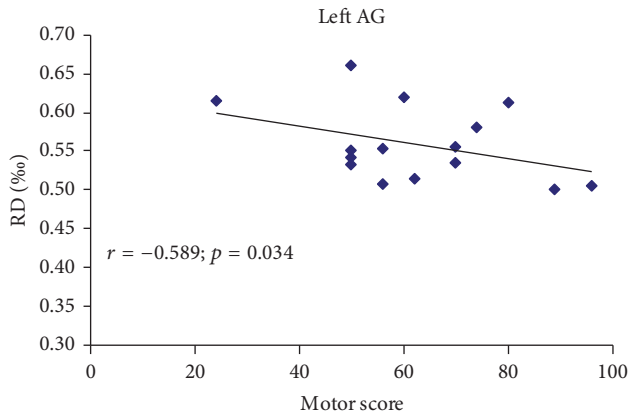

Figure 3: The correlation between diffusion metrics and clinical scores in SCI patients. Pearson correlation showed negative association between the RD of left AG and motor score of ASIA. ($r = -0.589$, $p = 0.034$; uncorrected). RD: radial diffusivity, AG: angular gyrus, ASIA: American Spinal Injury Association, SCI: spinal cord injury.

of SCI on the reorganization of the brain, which should be considered in future studies.

3.2. Differences in the WM Indices between the CSCI and ISCI Patients. Two-sample t-tests revealed no significant differences in the diffusion indices between the CSCI and ISCI patients, with the exceptions of relatively lower MD and lower AD values in the right CB of the CSCI relative to the ISCI patients ($p < 0.05$, uncorrected).

3.3. Correlations of the Clinical Variables with the Diffusion Indices in the SCI Patients. Partial correlation analyses revealed no correlations between any of the diffusion indices and the injury duration ($p > 0.05$, uncorrected; Supplementary Table S1). A negative correlation was observed between the RD values of the left AG and the motor scores ($r = -0.589$, $p = 0.034$; uncorrected; Figure 3).

4. Discussion

In the present study, decreased FA and increased RD were found in the distributed WM of the brain of the SCI patients; these changes occurred not only in the parts of the sensorimotor system that project to the regions of the spinal cord that innervate the paralyzed limbs but also in areas of the brain that are not directly involved in sensation or motor control. Moreover, no significant differences in any of the diffusion indices were found between the CSCI and ISCI patients. Finally, we observed negative correlations between the RD and the clinical scores that indicated an association between the brain WM integrity and clinical performance.

4.1. Brain WM Abnormalities in SCI Patients. To our knowledge, only a few studies have addressed the questions of whether and how WM changes occur in patients following SCI [8, 18–20, 27]. Our results were not consistent with those of Wei et al. [20] who failed to find any diffusion changes in the SCI patients without traumatic brain injury, while partially consistent with those of Wrigley et al. [8] and Freund et al. [27] who both detected decreased FA and/or increased MD in the sensorimotor pathway. The contradictory results between Wei et al. and us may be explained by the following factors: First is the difference of method: in Wei et al.'s study, they adopted TBSS as well as the ROI technique because TBSS alone did not find any between-group FA differences. They focused on five ROIs: ALIC, PLIC, forceps minor, gCC, and sCC. In addition, they combined bilateral brain structures into 1 ROI in the cross-subject comparisons (e.g., forceps minor, ALIC, and PLIC). It is possible that both TBI and SCI may cause unilateral changes in cerebral axonal organization or changes in other WM tracts. In the present study, we just used TBSS to assess between-group FA differences and found decreased fractional anisotropy (FA) in the left AG, right CB, left PreCG, left LOC, left SLF, left SMG, and left PostCG. Second, the difference in duration of SCI may be an important factor, because the degeneration processes of the injured ascending and descending fibres tracts are much slower in the central nerve system [28]. The SCI patients recruited in Wei et al.'s study were most subacute (mean injury duration of 93 days), while in the present study and in the studies by Wrigley et al. and Freund et al., most of the patients were chronic (mean injury duration 5.2 years, 12.5 years, and 14.6 years, resp.). Finally, the differences in imaging parameter of DTI might be another factor. The slice thickness of the DTI images by Wei et al. (5 mm) was much thicker than that of the present and other previous studies (below 2.5 mm); thus, partial volume effect might hide some tiny changes in the studies by Wei et al. Beside, the diffusion decoding directions of DTI by Wei et al. (15 directions) were much smaller than the present and other previous studies (30 to 64 directions). Previous studies have shown that higher number of diffusion decoding directions contributes to more robust calculation of diffusion indices [29]. It should be noted that, in the present study, we did not identify significant correlation between diffusion indices and injury duration, which was consistent with the finding by Freund et al. [27] in 2012. However, as we did not give a longitudinal study on the brain WM changes of SCI patients, the exact influence of duration of SCI on the changes of brain WM integrity should be further clarified in the future study.

Our present study demonstrated a significantly decreased FA in the sensorimotor WM that could be partially responsible for the anatomical changes in Somatosensory Cortex Area (S1) and Primary Motor Cortex Area (M1) [18, 30–39]. We also observed that the decrease in FA was primarily attributable to an increased RD rather than a change in the AD. Because RD increases are primarily caused by demyelination [40, 41], our findings are strongly suggestive of demyelination caused by secondary Wallerian degeneration or retrograde degeneration after SCI. Following secondary degeneration, disconnected sensorimotor areas are preserved, but their efferent motor commands do not reach the effectors, and they no longer receive appropriate afferent feedback, leading to severe sensorimotor function deficits [7, 38, 39].

Additionally, significant decrease in FA and increase in RD were observed in the CB. Because the CB has direct and indirect connections with the spinal cord, direct or transneuronal degeneration can explain this finding. The impaired CB WM is approximately located in the cerebellar crus VIII that is related to sensorimotor function. Thus, the degeneration of this CB region may be secondary to the injury of motor-related bundles of spinal cords. We did not find significant correlations between the changes in diffusion indices of CB and clinical sensory or motor measures, indicating that the secondary degeneration of the CB after SCI had little impact on the motor recovery. However, because we did not evaluate the fine motor/sensory skill of SCI patients, we cannot exclude the possible links between CB degeneration and these fine motor/sensory skills.

In addition to direct degeneration, SCI can also lead to transneuronal degeneration, which is related to regions such as the inferior parietal lobule (IPL), SLF, and LOC. The IPL contains AG and SMG and is involved in motor attention [42], motor planning [43], and action coding [44]. The degeneration of the IPL WM may account for the deficits in spatial positioning. SLF is the longest fibre tract among the association fibre bundles. This finding was consistent with that reported in 2013 by Yoon et al. [19]. The SLF connects the frontal lobe, parietal lobe, occipital lobe, and temporal lobe in the brain. Therefore, we hypothesized that the changes in SLF may result at least partially from the destruction of the functional connections between some regions in the brain. However, we did not investigate the changes in functional connection in our patients; therefore, the correlations between the SLP changes and functional connections in the brain cannot be confirmed. In the future, we will investigate this issue. The LOC is responsible for visual conduction. This finding cannot be reasonably explained and needs to be explored in future studies.

4.2. Differences in the Brain WM Abnormalities between the CSCI and ISCI Patients. It remains uncertain whether the degree of injury affects the WM changes. Although some studies have found WM changes in either CSCI or ISCI patients, no study has directly compared the potential differences between the two groups within a single study. For example, Villiger et al. [45] found significant white matter atrophy in the brainstem (medulla oblongata) and cerebellum (lobule IX) in ISCI patients, whereas Henderson et al. [18] reported that CSCI patients exhibited significantly reduced FA values in corticospinal tract, corticopontine tract, and superior cerebellum. In the present study, we directly compared the diffusion indices of the brain WM between CSCI and ISCI patients. Unfortunately, we found no significant differences in the diffusion indices between the CSCI and ISCI patients. We can provide the following possible interpretations for this result: (1) the transneuronal degeneration is nonspecific or microspecific in terms of CSCI and ISCI; (2) the sample sizes of each of the SCI subgroups were insufficient to detect the small differences in WM integrity between the CSCI and ISCI patients.

4.3. Correlations between the Clinical Variables and Diffusion Tensors in the SCI Group. A few studies have explored the correlations between WM changes and clinical variables and the results were controversial. Hou et al. [7] found no significant correlations between WM changes and clinical performances in SCI patients. However, Freund et al. [13] reported that SCI patients with greater corticospinal tract integrities exhibit better clinical recoveries than those with lower corticospinal tract integrities. In our current study, we found that greater WM integrity (lower RD) in the AG predicted better clinical performance. The AG is involved in motor attention [42], motor planning [43], and action coding [44]. Several previous reports have demonstrated that rehabilitation exercises following SCI can notably influence the structure and function of the brain [38, 46–49]. Thus, this association may indicate the potential of diffusion quantification for evaluating injury severity and predicting prognosis.

As the duration in the present study is heterogeneous, to eliminate its affects on our result, we made partial correlation analyses between the diffusion indices and the injury duration and found no significant differences, which was consistent with Hou et al. [7]. The negative correlation may be affected by the relative small sample size and the heterogeneous injured spinal segments.

5. Limitations

Several limitations of the present study should be addressed when interpreting the results. First, the current study investigated WM changes in SCI patients with a very broad range of disease durations. Second, the injured spinal segments were heterogeneous. Finally, the relative small sample size diminished the statistical power, particularly when we considered the CSCI and ISCI patients as separate groups.

6. Conclusions

In conclusion, our findings provide evidence that SCI can cause changes in the brain's WM that are not limited to the sensorimotor system, which directly innervates the paralyzed limbs but includes brain areas without such direct connections. Additionally, the changes of the WM integrity in the brain can predict clinical performance. Moreover, the severities of the impairments in the brain's WM are similar between CSCI and ISCI patients. These findings indicate the potential of using diffusion indices in investigations of secondary WM impairments and the prediction of the prognoses of SCI. The affection of left AG on rehabilitation therapies needs to be further researched in the future.

Competing Interests

The authors declare no competing financial interests.

Authors' Contributions

Weimin Zheng and Qian Chen contributed equally to this work in terms of (1) the conception or design of the work; (2)

the acquisition, analysis, and the interpretation of data for the work; (3) drafting the work; (4) final approval of the version to be published; (5) agreement to be accountable for all aspects of the work. Xin Chen, Lu Wan, Wen Qin, and Zhigang Qi contributed to (1) the analysis data for the work; (2) drafting the work; (3) final approval of the version to be published; (4) agreement to be accountable for all aspects of the work. Nan Chen contributed to (1) the design of the work; (2) revising the work; (3) final approval of the version to be published; (4) agreement to be accountable for all aspects of the work. Kuncheng Li contributed to (1) revising the work; (2) final approval of the version to be published; (3) agreement to be accountable for all aspects of the work.

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Research Article

Altered Brain Functional Activity in Infants with Congenital Bilateral Severe Sensorineural Hearing Loss: A Resting-State Functional MRI Study under Sedation

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Early hearing deprivation could affect the development of auditory, language, and vision ability. Insufficient or no stimulation of the auditory cortex during the sensitive periods of plasticity could affect the function of hearing, language, and vision development. Twenty-three infants with congenital severe sensorineural hearing loss (CSSHL) and 17 age and sex matched normal hearing subjects were recruited. The amplitude of low frequency fluctuations (ALFF) and regional homogeneity (ReHo) of the auditory, language, and vision related brain areas were compared between deaf infants and normal subjects. Compared with normal hearing subjects, decreased ALFF and ReHo were observed in auditory and language-related cortex. Increased ALFF and ReHo were observed in vision related cortex, which suggest that hearing and language function were impaired and vision function was enhanced due to the loss of hearing. ALFF of left Brodmann area 45 (BA45) was negatively correlated with deaf duration in infants with CSSHL. ALFF of right BA39 was positively correlated with deaf duration in infants with CSSHL. In conclusion, ALFF and ReHo can reflect the abnormal brain function in language, auditory, and visual information processing in infants with CSSHL. This demonstrates that the development of auditory, language, and vision processing function has been affected by congenital severe sensorineural hearing loss before 4 years of age.

1. Introduction

Individuals with congenital sensorineural hearing loss usually have no hearing experiences after birth. Approximately 1‰ to 6‰ newborns suffered from severe to profound sensorineural hearing loss [1–5]. Early hearing deprivation could affect not only language but also cognitive functions, such as decreased execution function, disturbed personality, abnormal social behavior, and delayed decision-making and enhanced visual attention [6–14]. However, the mechanisms of changes in language functions and cognitive functions after hearing loss need further evidence to support.

There is the cross-modal reorganization of auditory-related brain area after long-term hearing deprivation [5, 15]. Functional reorganization of auditory cortex in the patients with hearing loss has been reported by many researchers and the auditory cortex in the deaf could be activated by nonauditory stimulation, such as visual, speech, and vibrotactile stimulation [15–19]. Pathologically, the volume and size of the neurons of cochlear nucleus in deaf animal models are decreased depending on the onset and duration hearing loss [20, 21]. The functional changes of auditory-related brain area remain largely unknown.

Brain development is a gradual process of unfolding of a self-organizing and highly synchronous network from complex interactions between internal and external environment. The studies from both animal models and human children have demonstrated that the maturation of auditory cortex is critical at the first few years of life [22, 23]. Lots of cerebral functions, such as auditory sensory and language, have shown sensitive period. Insufficient or no stimulation of the cortex during the sensitive periods of plasticity could lead to the abnormal function of auditory and language development. Oral speech and language skills would be affected in late-implanted children [24, 25]. The intrinsic mechanisms for language acquisition ability with age in congenital deaf children need to be further investigated.

The advances of fMRI had made it possible to study the intrinsic functional organization of the brain. For example, resting-state fMRI could be used to investigate the spatial-temporal correlations within the functional brain regions during rest, especially in the deaf children who could not cooperate the other kinds of task performance. The amplitude of low frequency fluctuations (ALFF) is one of the parameters to measure the total power in the range of 0.01 and 0.1 Hz which could be an index to reflect the neurophysiological changes in different brain diseases [26–30]. Regional homogeneity (ReHo) reflects the similarities or synchrony of low frequency bold signal fluctuations across the intraregional brain. ReHo, the brain activities as clusters, could change in the different brain disease, such as neuromyelitis optical, stroke, Parkinson, hepatic encephalopathy, and Alzheimer's disease. But until now, little information is available about the changes of intrinsic brain activity in the infants with congenital hearing loss. Here, we hypothesized that there are ALFF and ReHo changes in auditory sensory, language, and vision related brain areas due to congenital hearing loss.

This study aimed to use resting-state functional MRI to study the intrinsic functional changes of brain area due to auditory deprivation in infants with congenital severe sensorineural hearing loss.

2. Materials and Methods

2.1. Participants. A total of 23 infants with congenital severe sensorineural hearing loss (CSSHL) who did not pass hearing screening using auditory brain stem response (ABR) test at 3 days and 42 days after birth were retrospectively included in our study. The ABR results of all infants showed greater than 90 dB which indicates severe or profound sensorineural hearing loss. The age of deaf infants at MRI examination was from 6 months to 48 months (mean age 24.18 ± 14.00 months). Seventeen age and sex matched normal hearing subjects were recruited. The age of the control group at MRI examination was from 11.2 months to 49 months (mean age 26.35 ± 12.67 months). Excluding criteria include a variety of central nervous system diseases, such as white matter hypoplasia, abnormal neuronal migration, and neuronal skin syndrome, tumor, trauma, infection, epilepsy, and so on. Informed consent was signed by the parents of the infants and all the examinations were approved by the hospital ethics committee.

2.2. fMRI Data Acquisition. All the subjects were scanned with MRI at the 3.0T MR scanner (Siemens, Trio) and 16-channel standard quadrature head coil. Before MRI examination, all the infants were given the oral administration of 10% chloral hydrate with an amount of 0.6 mL per kg and the maximum amount of no more than 80 mL.

The detailed MRI sequences include the following: firstly, spin echo (spin echo, SE) and fast spin echo (fast spin echo, FSE) and whole brain T1WI and T2WI were acquired to exclude central nervous system abnormalities. The parameters were as follows: T1WI: TR/TE = 300/2.5 ms, slice thickness = 4 mm, the interlayer spacing = 1.2 mm, matrix = 320 × 320, FOV = 220 × 220 mm, flip angle = 70°, NEX = 1,25 transverse slices covering the whole brain, T2WI: TR/TE = 6000/93 ms, slice thickness = 4 mm, the interlayer spacing = 1.2 mm, matrix = 320 × 320, FOV = 220 × 220 mm, and flip angle = 120°. Secondly, gradient-echo echo planar imaging (GRE-EPI) was scanned and the detailed parameters are TR/TE = 3000 ms/30 ms, FOV = 220 × 220 mm, flip angle = 90°, matrix = 64 × 64, slice thickness = 3 mm, 210 frames, and 38 transverse slices without gap covering the whole brain. Finally, magnetization prepared rapid gradient echo imaging (MP-RAGE) sequences. The parameters were set as follows: TR/TE = 1900/2.53 ms, FOV = 250 × 250 mm, flip angle = 9°, matrix = 256 × 256, slice thickness = 1 mm, and 160 sagittal slices without gap covering the whole brain.

2.3. fMRI Data Analysis. The resting-state fMRI data were preprocessed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and a pipeline analysis toolbox, REST, and DPARSF (http://www.restfmri.net/) [31–34]. The first ten volumes were discarded. The remaining images were preprocessed using a procedure, which included slice timing correction, head motion correction, T1-weighted image-based spatial normalization to the Montreal Neurological Institute (MNI) space, linear trend removal, and bandpass filtering (0.01–0.08 Hz). All the participants' head motion parameters were less than 3 mm in translation and less than 3 degrees in rotation. We orthogonalized each within-brain voxel's time series with respect to the mean time series from the subject's WM, CSF signals, and the six head motion parameters corresponding to the subject as well as linear and quadratic trends. Average WM and CSF segmentations across all subjects were computed in MNI space. ALFF and ReHo were computed by REST software (http://resting-fmri.sourceforge.net). Finally, the images were smoothed with a Gaussian filter of 6 mm full width at half maximum (FWHM). Template selected was infant template (using 9–15-month-old infant template) provided by the Imaging Research Center (https://irc.cchmc.org/software/infant.php).

2.4. Statistics Analysis. Two-sample t-test was conducted based on the ALFF and ReHo maps by REST software. Age and gender were selected as covariates. AlphaSim corrected $p < 0.05$ (cluster size > 228 voxels). Correlation analysis was performed to calculate the relationship between ALFF and age in two groups by using SPSS version 19.0 (SPSS Inc. Chicago, IL). Significant difference was set at $p < 0.05$. The value of Cohen d was used to describe the effect size (ES).

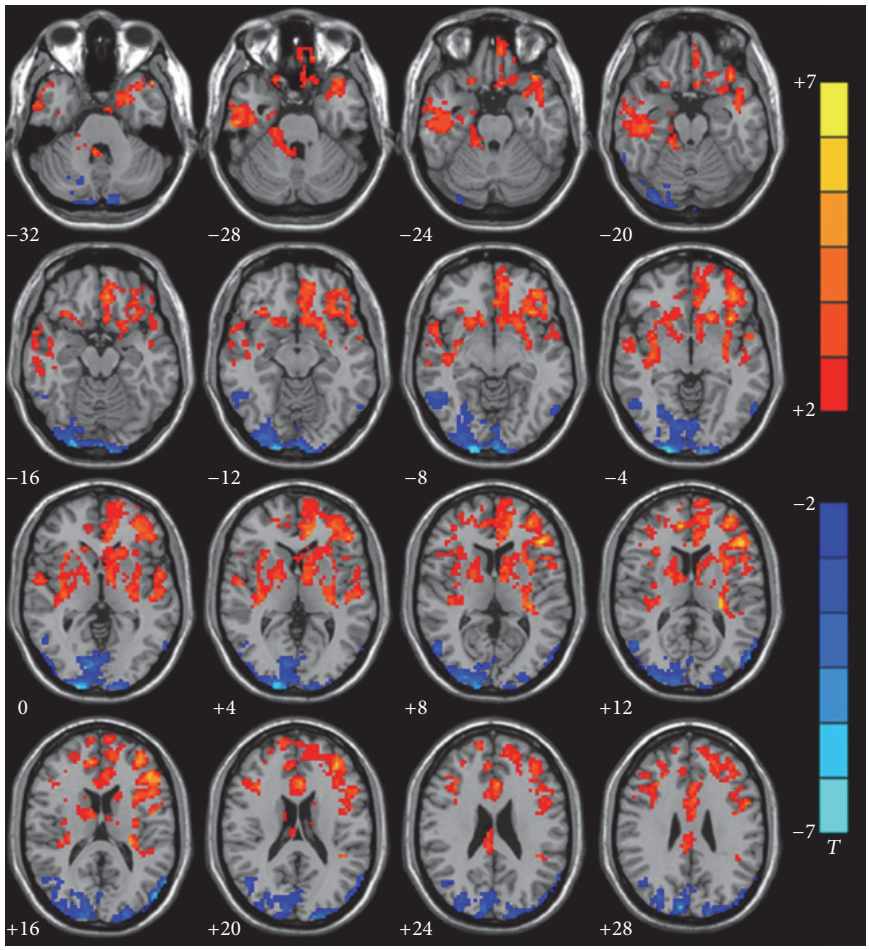

Figure 1: Group analysis of ALFF between infants with CSSHL and healthy controls. Compared with the control group, decreased (red) ALFF was observed in left Heschl's gyri (BA41) ($p = 0.0059$, ES = 0.94), left superior temporal gyrus (BA22) ($p = 0.0003$, ES = 1.27), left inferior frontal gyrus (BA44) ($p = 0.0004$, ES = 1.27), left inferior frontal gyrus (BA45) ($p = 0.0000$, ES = 2.18), left inferior prefrontal gyrus (BA47) ($p = 0.0001$, ES = 1.40), and left dorsolateral prefrontal cortex (BA46) ($p = 0.0000$, ES = 1.68). Increased (blue) ALFF was observed in right occipital lobe and right angular gyrus, which included BA18 ($p = 0.0022$, ES = −1.07), BA19 ($p = 0.0027$, ES = −1.04), BA17 ($p = 0.0000$, ES = −1.46), and BA39 ($p = 0.0020$, ES = −1.08). AlphaSim corrected ($p < 0.05$, cluster size > 228 voxels). The significance level of activity was indicated by the color bar (T), increasing as red proceeding to yellow decreasing as blue to cyan.

3. Results

3.1. ALFF in Infants with CSSHL. ALFF differed significantly between the deaf and hearing group in left Heschl's gyri (BA41) ($p = 0.0059$, ES = 0.94), left superior temporal gyrus (BA22) ($p = 0.0003$, ES = 1.27), left inferior frontal gyrus (BA44) ($p = 0.0004$, ES = 1.27), left inferior frontal gyrus (BA45) ($p = 0.0000$, ES = 2.18), left inferior prefrontal gyrus (BA47) ($p = 0.0001$, ES = 1.40), and left dorsolateral prefrontal cortex (BA46) ($p = 0.0000$, ES = 1.68) in infants with CSSHL (deaf < hearing), which are responsible for auditory, language, and executive function.

ALFF value also differed significantly between the deaf and hearing group in right occipital lobe and right angular gyrus, which included right BA18 ($p = 0.0022$, ES = −1.07), right BA19 ($p = 0.0027$, ES = −1.04), right BA17 ($p = 0.0000$, ES = −1.46), and right BA39 ($p = 0.0020$, ES = −1.08) (deaf > hearing), which are responsible for processing visual information (Figure 1, Table 1).

3.2. ReHo in Infants with CSSHL. ReHo differed significantly between the deaf and hearing group in left superior temporal gyrus (BA22) ($p = 0.0117$, ES = 0.86), left inferior frontal gyrus (BA45) ($p = 0.0038$, ES = 1.00), left inferior prefrontal gyrus (BA47) ($p = 0.0016$, ES = 1.10), left dorsolateral prefrontal cortex (BA46) ($p = 0.0076$, ES = 0.91), left medial frontal gyrus (BA32) ($p = 0.003$, ES = 1.03), and left temporal polar gyrus (BA38) ($p = 0.0102$, ES = 0.88) (deaf < hearing), which are responsible for auditory processing, language perception, executive function, and behavior and decision-making.

ReHo value also differed significantly between the deaf and hearing group in left occipital lobe which included BA18

Table 1: Comparison of ALFF differences between infants with CSSHL and hearing controls.

Region	H	BA	Volume (mm^3)	Coordinates			Peak	p	ES
				X	Y	Z	T-value		
Deaf < control									
Heschl's gyrus	L	41	10	−41	−40	18	2.92	0.0059*	0.94
Superior temporal gyrus	L	22	16	−56	−17	3	3.93	0.0003*	1.27
Inferior frontal gyrus	L	44	20	−52	14	17	3.91	0.0004*	1.27
Inferior frontal gyrus	L	45	10	−44	30	10	6.73	0.0000*	2.18
Inferior prefrontal gyrus	L	47	62	−42	38	−2	4.33	0.0001*	1.40
Dorsolateral prefrontal gyrus	L	46	28	−36	51	17	5.19	0.0000*	1.68
Deaf > control									
Occipital gyrus	R	18	278	12	−81	−4	−3.29	0.0022*	−1.07
Occipital gyrus	R	19	165	27	−68	−4	−3.21	0.0027*	−1.04
Middle occipital gyrus	R	17	73	11	−87	1	−4.49	0.0000*	−1.46
Angular gyrus	R	39	31	45	−66	22	−3.32	0.0020*	−1.08

CSSHL: congenital severe sensorineural hearing loss; H, hemisphere; L, left; R, right; BA, Brodmann's area. AlphaSim corrected ($p < 0.05$, voxel-level cut-off); ES, value of Cohen d was used to describe the effect size. * Indicating the significant difference compared with controls.

Table 2: Comparison of ReHo differences between infants with CSSHL and hearing controls.

Region	H	BA	Volume (mm^3)	Coordinates			Peak	p	ES
				X	Y	Z	T-value		
Deaf < control									
Superior temporal gyrus	L	22	14	−56	−17	3	2.65	0.0117*	0.86
Inferior frontal gyrus	L	45	19	−44	−30	10	3.08	0.0038*	1.00
Inferior prefrontal gyrus	L	47	74	−42	38	−2	3.40	0.0016*	1.10
Dorsolateral prefrontal gyrus	L	46	18	−36	51	17	2.82	0.0076*	0.91
Medial frontal gyrus	L	32	45	−11	45	9	3.17	0.0030*	1.03
Temporal pole	L	38	52	−30	18	−31	2.70	0.0102*	0.88
Deaf > control									
Occipital gyrus	R	18	243	−7	−66	1	−2.81	0.0078*	−0.91
Occipital gyrus	R	19	195	−8	−87	27	−3.71	0.0006*	−1.20
Medial occipital gyrus	R	17	33	−2	−97	4	−4.35	0.0000*	−1.41

CSSHL: congenital severe sensorineural hearing loss; H, hemisphere; L, left; R, right; B, bilateral; BA, Brodmann's area. AlphaSim corrected ($p < 0.05$, voxel-level cut-off); ES, value of Cohen d was used to describe the effect size. * Indicating the significant difference compared with controls.

($p = 0.0078$, ES = −0.91), BA19 ($p = 0.0006$, ES = −1.20), and BA17 ($p = 0.0000$, ES = −1.41) (deaf > hearing), which are responsible for visual information processing (Figure 2 and Table 2).

3.3. Relationship between ALFF and Age in Auditory, Language, and Vision Related Brain Areas in Infants with CSSHL. The significant increase and decrease ALFF of auditory, language, and visual perception related brain areas were selected as region of interest (ROI) in both groups, which included left BAs 22, 41, 44, 45, 46, and 47 and right BAs 18, 19, and 39. The correlation between ALFF of these ROIs and age was calculated. ALFF of left BA45 was negatively correlated with age and showed a decreasing trend in the deaf group along with age increased ($r = -0.568$, $p = 0.005$), but it showed an increased trend in the control group, though there is no significant correlation ($r = 0.171$, $p = 0.512$) (Figure 3). ALFF of right BA39 was positively correlated with age and showed an increasing trend in deaf group with age ($r = 0.574$, $p = 0.004$). However, there was no significant correlation in control group ($r = -0.229$, $p = 0.378$) (Figure 4).

ALFF value of left BA47 was positively correlated with age and showed an increasing trend in the control group ($r = 0.530$, $p = 0.029$), but it showed no significant correlation in the deaf group ($r = -0.003$, $p = 0.989$) (Figure 5). There was no significant correlation between other ROIs and age in both groups ($p > 0.05$). All above results indicated that the function of auditory, language, and vision was changed in infants with CSSHL.

4. Discussion

Changes of intrinsic brain organization are essential for exploring infants with the congenital severe sensorineural hearing loss (CSSHL). This is the first study using resting-state fMRI to evaluate the function of auditory and language-related brain areas in infants with CSSHL before four years of age. There were some important findings. ALFF and ReHo

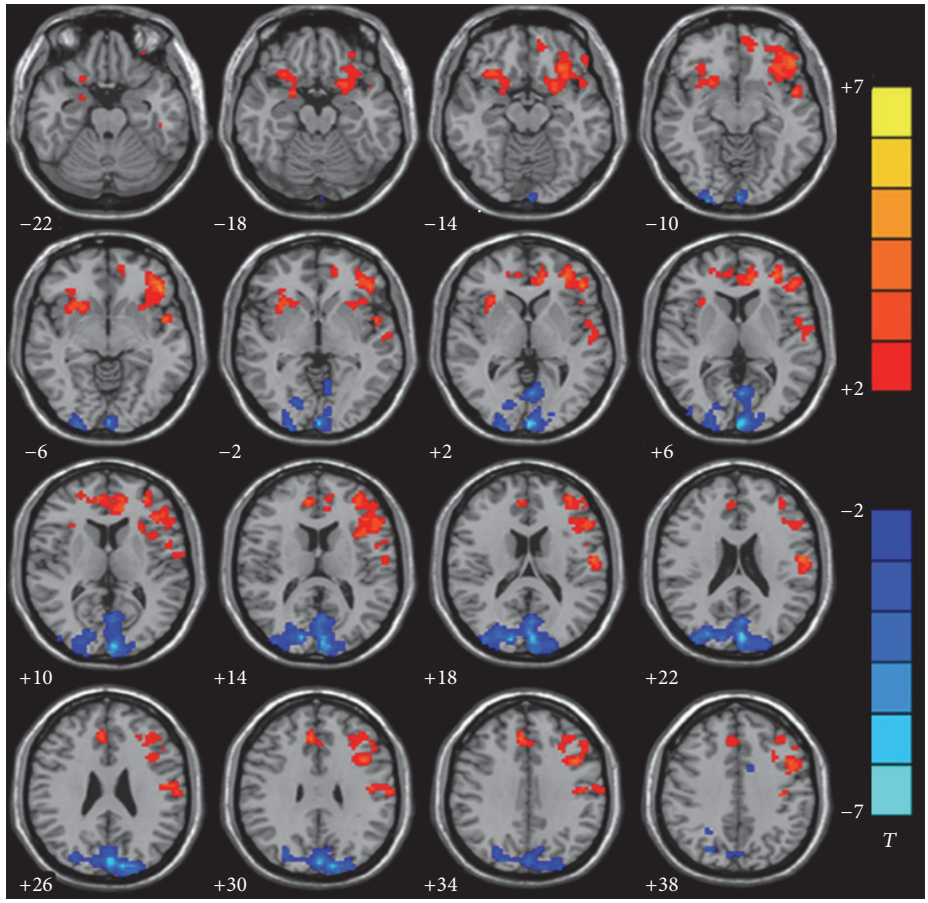

Figure 2: Group analysis of ReHo between infants with CSSHL and healthy controls. Compared with control group, decreased (red) ReHo was observed in left superior temporal gyrus (BA22) ($p = 0.0117$, ES = 0.86), left inferior frontal gyrus (BA45) ($p = 0.0038$, ES = 1.00), left inferior prefrontal gyrus (BA47) ($p = 0.0016$, ES = 1.10), left dorsolateral prefrontal cortex (BA46) ($p = 0.0076$, ES = 0.91), left medial frontal gyrus (BA32) ($p = 0.0030$, ES = 1.03), and left temporal polar gyrus (BA38) ($p = 0.0102$, ES = 0.88). Increased (blue) ReHo was observed in left occipital lobe which included BA18 ($p = 0.0078$, ES = −0.91), BA19 ($p = 0.0006$, ES = −1.20), and BA17 ($p = 0.0000$, ES = −1.41). AlphaSim corrected ($p < 0.05$, cluster size > 228 voxels). The significance level of activity was indicated by the color bar (T), increasing as red proceeding to yellow decreasing as blue to cyan.

values in the deaf infants decreased in auditory, language processing, and executive function related brain areas. ALFF and ReHo values in the deaf infants increased in occipital lobe, which is responsible for visual information processing. Another important finding was that the changes of ALFF of left BA45 were positively correlated with deaf during, and ALFF of right BA39 was negatively correlated with deaf duration in infants with CSSHL. ALFF of left BA47 was also found positively correlated with age in normal subjects again, but the correlation disappeared in infants with CSSHL.

ALFF indirectly reflects the spontaneous neural activity and indicates the functional changes of brain activity [35, 36]. In the present study, ALFF in infants with CSSHL was found decreased in Heschl's gyrus and superior temporal gyrus, inferior frontal lobe, angular gyrus, temporal polar gyrus, and inferior and dorsolateral prefrontal gyrus, which contains BA22, BA41, BA44, BA45, BA46, and BA47, which are responsible for the auditory processing and language perception. The results suggested that the function of auditory and language-related brain cortex was affected due to no sound stimulated. The previous literature also reported that the patients with a profoundly sensorineural hearing loss could have problems in language and learning ability [37–39]. ReHo indicates that topical functional brain area is in a similar activity and abnormal ReHo reflects the desynchronized brain activity [40, 41]. In the present study, ReHo significantly decreased in superior temporal gyrus, inferior frontal gyrus, inferior prefrontal gyrus, dorsolateral prefrontal cortex, and temporal polar gyrus, which contains BA22, BA45, BA47, BA46, BA32, and BA38, in infants with CSSHL. The results also demonstrated that function of auditory and language-related cortex was impaired due to sensorineural hearing loss. It was also reported that glucose hypometabolism was observed in auditory and language-related cortex [42]. Decreased ReHo could reflect the desynchronized blood flow which indicated reduced gray matter concentration [40, 43]. Patients with sensorineural hearing loss have shown lots of brain areas with thinning cortical thickness [44].

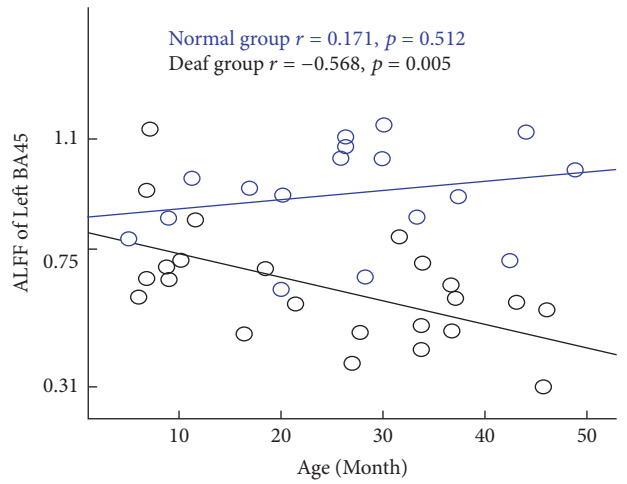

Figure 3: Significant negative correlation between age and the value of ALFF in left BA45 responsible for language production in the deaf group. Deaf group: black ($r = -0.568$, $p = 0.005$). There was a trend of increase along with the increase of age. No significant correlation was found in the control group. Control group: blue ($r = 0.171$, $p = 0.512$).

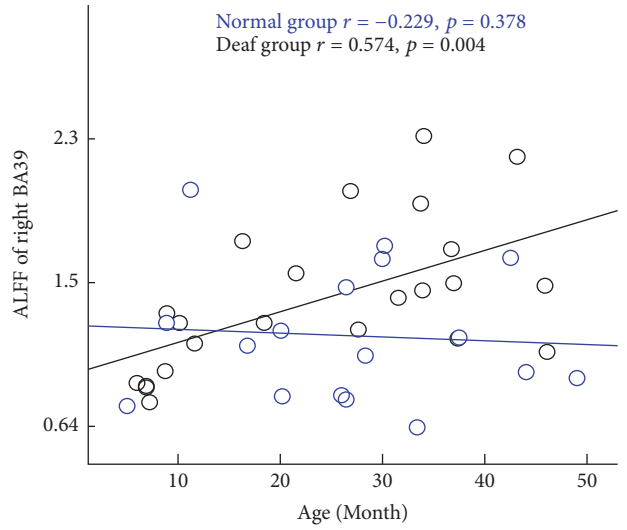

Figure 4: Significant positive correlation between age and the value of ALFF in right BA39 responsible for language processing, spatial orientation, and semantics in the deaf group. Deaf group: black ($r = 0.574$, $p = 0.004$). No significant correlation was observed in the control group. Control group: blue ($r = -0.229$, $p = 0.378$).

The thickness of auditory cortex decreased due to hearing loss and the deafness degree was correlated with the time of deafness onset.

Executive function includes lots of organizational and self-regulatory skills, such as personal and social behavior, decision-making, and emotional and cognitive processing [6, 45] In the present study, ALFF and ReHo were found decreased in inferior prefrontal gyrus (BA47) and dorsolateral prefrontal cortex (BA46), which are responsible for executive function. It suggests that the executive function

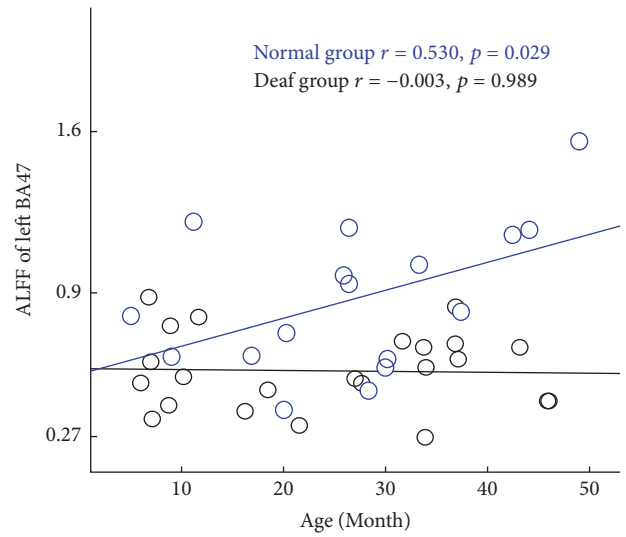

Figure 5: Significant positive correlation between age and the value of ALFF in left BA47 of the control group. Control group: blue ($r = 0.530$, $p = 0.029$). Deaf group: black ($r = -0.003$, $p = 0.989$). No significant correlation was found in the deaf group.

was abnormal in the infants with CSSHL. Impairment of language function in the deaf children could result in the impaired executive function which could negatively impact the development of language [6].

In deaf infants, not all the executive functions were impaired; some of them are preserved and even enhanced [6, 46, 47]. In the present study, ALFF was found to be increased in right angular gyrus (BA39), which indicated that the spatial orientation and semantic sensation were enhanced compared to the hearing subjects. The study also found that the ability of tracking objects and orientating was enhanced in deaf subjects [12, 13].

The right occipital gyri (BA18, BA19, and BA17) are responsible for visual information processing. In the present study, both ALFF and ReHo values of BA18, BA19, and BA17 increased. It suggests that the vision function had been enhanced due to the hearing loss. Another study also suggested the compensatory enhanced visual process after auditory deprivation, and meanwhile vision cortex is much more sensitive to reorganization or neuroplasticity without auditory input [11, 48]. Behavioral studies had also shown that deaf people have better visual performance [49]. It indicates that vision function is enhanced due to vision cortex reorganization. Neuroplasticity based on the sensory stimulation is present throughout the whole life and the development of the cortex is largely depending on the environment [50]. The sensory cortex and other associated systems, such as cognitive and language, not only interact with each other but also adjust functional characterization according to the stimulation and experience [51].

Interestingly, the significant correlation was found between ALFF of left BA45, right BA39, and deafness duration in deaf infants. ALFF of left BA45 was found to be negatively correlated with the deprivation duration in deaf

infants. In contrast, no significant correlation was found between ALFF of left BA45 and age in normal controls although there was an increasing trend along with aging. This demonstrated that the function of left BA45 which is related to language was impaired more seriously along with deaf duration. ALFF of right BA39 was found to be positively correlated with the deprivation duration in deaf infants but with no significant correlation with age in hearing infants. The cortex is responsible for spatial orientation and semantic sensation. This suggests that the function of spatial orientation and semantic sensation was enhanced along prolonged deafness duration. Significant positive correlation was found between ALFF of left BA47 and age in normal infants, but no correlation was found in deaf infants. It may conclude that the function of left BA47 is enhanced along with age increasement in normal infants, but this increased trend disappeared in deaf infants, which suggests that the executive function is the cross-modal plasticity caused by the deprivation of auditory experience.

The primary limitation of this study was the small sample size of infants (hearing loss and hearing group). Additionally, clinical information about the function of auditory and language recovery in deaf infants with cochlear implant was not followed up. The correlation between the recovery and abnormal function of auditory and language-related brain areas in deaf infants' precochlear implant needs to be investigated in the future study.

5. Conclusion

In conclusion, ALFF and ReHo reflect the abnormal brain function in language, auditory, and visual information processing in infants with CSSHL before 4 years of age. Congenital severe sensorineural hearing loss affected the development of auditory and language processing function.

Competing Interests

The authors declare that there are no competing interests regarding the publication of this paper.

Authors' Contributions

Shuang Xia, Qiang Li, and Wen Shen designed the research; Meizhu Zheng and TianBin Song performed the experiment; TianBin Song, Jing Che, and Chao Chai analyzed the data; Shuang Xia and TianBin Song wrote the paper. Shuang Xia and TianBin Song contributed equally to this work.

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Review Article

Hybrid Assistive Neuromuscular Dynamic Stimulation Therapy: A New Strategy for Improving Upper Extremity Function in Patients with Hemiparesis following Stroke

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Hybrid Assistive Neuromuscular Dynamic Stimulation (HANDS) therapy is one of the neurorehabilitation therapeutic approaches that facilitates the use of the paretic upper extremity (UE) in daily life by combining closed-loop electromyography- (EMG-) controlled neuromuscular electrical stimulation (NMES) with a wrist-hand splint. This closed-loop EMG-controlled NMES can change its stimulation intensity in direct proportion to the changes in voluntary generated EMG amplitudes recorded with surface electrodes placed on the target muscle. The stimulation was applied to the paretic finger extensors. Patients wore a wrist-hand splint and carried a portable stimulator in an arm holder for 8 hours during the daytime. The system was active for 8 hours, and patients were instructed to use their paretic hand as much as possible. HANDS therapy was conducted for 3 weeks. The patients were also instructed to practice bimanual activities in their daily lives. Paretic upper extremity motor function improved after 3 weeks of HANDS therapy. Functional improvement of upper extremity motor function and spasticity with HANDS therapy is based on the disinhibition of the affected hemisphere and modulation of reciprocal inhibition. HANDS therapy may offer a promising option for the management of the paretic UE in patients with stroke.

1. Functional Recovery of Upper Extremity Motor Function following Stroke

Stroke is a common health-care problem that causes physical impairment, disability, and problems in social participation. The most common impairment caused by stroke is motor impairment. Motor impairment affects the control of the unilateral upper and lower extremities. Recovery of function in the hemiparetic upper extremity is noted in fewer than 15% of patients after stroke [1].

Patients often compensate for their paretic upper extremity by using their intact upper extremity in the performance of everyday tasks [2]. It is supposed that strong reliance on compensatory overuse of the intact upper extremity inhibits functional recovery of the impaired upper extremity. This may explain the limited improvement of the functional capability of the paretic upper extremity in activities of daily living (ADL).

Principles of motor rehabilitation following stroke have been described as being dose-dependent and task-specific [3]. High-intensity practice and task-specific training are recommended for functional recovery. Several systematic reviews [4, 5] have explored whether high-intensity therapy improves recovery, and the principle that increased intensive training is helpful is widely accepted. Task-specific training is a well-accepted principle in motor rehabilitation. Training

should target the goals that are relevant for the needs of the patients and preferably be given in the patient's own environment.

The goal of upper extremity rehabilitation is to improve the capability of the paretic upper extremity for ADL. Constraint-induced movement therapy (CIMT) has been developed to enhance the forced use of the paretic hand in ADL with reduction of the compensatory overuse of the intact upper extremity. However, to participate in CIMT, the candidates must be able to voluntary extend their fingers and wrist at least 10 degrees, practice for 6 hours daily in a 2-week course, and spend waking hours with their nonparetic hand in a mitt [6].

To counter potential problems inherent in the intensive services needed for CIMT, we developed an alternative therapeutic approach that provides high-intensity training to facilitate the use of the paretic upper extremity in daily living by combining closed-loop electromyography- (EMG-) controlled neuromuscular electrical stimulation (NMES) with a wrist-hand splint for patients with moderate to severe hemiparesis. Fujiwara et al. called this hybrid assistive neuromuscular dynamic stimulation (HANDS) therapy [7].

2. HANDS Therapy

A PubMed literature search was conducted using the MeSH terms stroke, rehabilitation, upper extremity function, and neuromuscular electrical stimulation, and 71 articles were identified. A further search of PubMed with the terms stroke, rehabilitation, upper extremity function, neuromuscular electrical stimulation, and splint identified 4 articles, all regarding HANDS therapy.

HANDS therapy facilitates the use of the paretic upper extremity in daily living by combining closed-loop EMG-controlled NMES with a wrist-hand splint for patients with moderate to severe hemiparesis. This HANDS system is active for 8 hours, and patients are instructed to use their paretic hand as much as possible while wearing the HANDS system. Their nonparetic upper extremity is not restrained. The patients are also instructed to practice bimanual activities in their ADL. All participants in HANDS therapy are admitted, and the length of the intervention is 21 days. They receive 90 minutes of occupational therapy per day, 5 days a week. Each session of occupational therapy consists of gentle stretching exercise of the paretic upper extremity and active muscle reeducation exercise. All participants are instructed how to use their paretic hand in ADL with the HANDS system. Occupational therapists are directed toward participants' goals and focused on their particular impairments and disabilities; thus, the specific therapy that each patient receives varies [7, 8].

Fujiwara et al. [7, 8] reported the indications for HANDS therapy as follows: (1) no cognitive deficits; (2) no pain in the paretic upper extremity; (3) passive extension range of motion (ROM) greater than 0 degrees of the affected wrist and −10 degrees of the metacarpophalangeal joints; (4) detectable surface EMG signals in the affected extensor digitorum communis (EDC) or extensor pollicis longus (EPL) when the patient intends to extend their fingers; (5) ability to raise the paretic hand to the height of the nipple; (6) scores of Fugl-Meyer test position sense of joints in the glenohumeral joint, elbow, wrist, and thumb of 1 or more; and (7) the ability to walk without physical assistance in daily life (e.g., including patients who can walk independently with a cane and/or an orthosis). The exclusion criteria were (1) history of major psychiatric or previous neurological disease, including seizures; (2) cognitive impairment precluding appropriately giving informed consent or the patient's Mini Mental Examination Scale score was below 25; (3) patients with severe pain in the paretic upper extremity; (4) patients with a pacemaker or other implanted stimulator; and (5) patients with visuospatial neglect or apraxia.

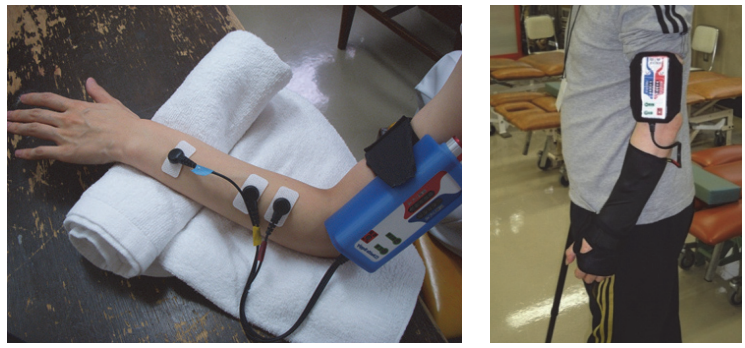
Previous reports showed that none of the patients experienced any discomfort or significant disability with the HANDS therapy.

2.1. Closed-Loop Electromyography- (EMG-) Controlled Neuromuscular Electrical Stimulation (NMES). Twenty-nine articles were found in PubMed using the terms stroke, electromyography, neuromuscular electrical stimulation, and upper extremity. Thirteen of 29 articles were on EMG-triggered NMES. Six of 29 articles were on EMG-controlled NMES. Two involved contralaterally controlled electrical stimulation.

EMG-triggered NMES applies preset electrical stimulation when EMG activity reaches a target threshold. The stimulus intensity and duration are determined and not changeable. EMG-controlled NMES applies electrical stimulation during voluntary contraction and changes the stimulation intensity in proportion to the changes in EMG amplitude.

For assistive stimulation, HANDS therapy used closed-loop EMG-controlled NMES, which was developed by Muraoka [9] and commercially available with MURO stimulation (Pacific Supply, Osaka, Japan). This closed-loop EMG-controlled NMES is portable and attaches to the arm (Figure 1). The surface electrodes pick up EMG signals at the target muscle and simultaneously stimulate it in direct proportion to the picked-up EMG signal, with the exception of the 25 ms after delivering each stimulation pulse, in which stimulation artifacts and M wave are observed. The external adjustment unit sets (1) range of stimulus intensity; (2) sensitivity of the EMG; (3) threshold of EMG amplitude that starts stimulation; and (4) gradient of stimulus intensity change to the change of EMG amplitude. Once these parameters were set with the external adjustment unit, the stimulator memorized these parameters.

It is difficult for patients with severe to moderate hemiparesis to extend their paretic fingers. As for hand function to perform ADL, pinch and release, and grip and release, are key functions. It is necessary to restore finger extension to perform ADL with the paretic upper extremity in patients with severe to moderate hemiparesis. To restore finger extension, electrical stimulation is applied to finger extensors in HANDS therapy. A pair of electrodes for EMG detection and stimulation (10 mm diameter) placed 20 mm apart on the



(a) (b)

Figure 1: (a) Closed-loop electromyography- (EMG-) controlled neuromuscular electrical stimulation (NMES). A pair of electrodes for EMG detection and stimulation are placed on the affected extensor digitorum communis muscle, and one electrode for stimulation is placed on the affected extensor indicis muscle. (b) Participants wear a wrist-hand splint and carry a closed-loop EMG-controlled NMES with arm holder for 8 hours during the daytime.

affected EDC and one electrode (10 mm) for stimulation are placed on the affected EI.

The EMG data and amount of stimulation were recorded with an attached data-logger system of the MURO device while the participants wore the MURO device. The participant's compliance with wearing the device for 8 hours during the daytime can be monitored using this data-logger system in HANDS therapy.

2.2. Splint. The patients wear a wrist-hand splint (Wrist Support, Pacific Supply Co.) and carry a portable closed-loop EMG-controlled NMES with arm holder for 8 hours during the daytime. The rationale for combining the stimulation system with a wrist-hand splint was derived from the work of Fujiwara et al. [10]. They showed that wearing a wrist-hand splint reduced spinal motoneuron excitability and flexor muscle overactivity during voluntary finger extension. During finger extension, muscle activities of the finger flexors, wrist flexors, and elbow flexors were reduced with the wrist-hand splint. The wrist-hand splint effect on the elbow flexors was supposed to be mediated by secondary afferent inhibition [11].

The wrist-hand splint also makes the hand shape functional. Hand shape is important for hand function. The hand has longitudinal and transverse arches. These arches are important for holding, and thumb opposition and the web space are important for pinching. A wrist-hand splint helps to form the longitudinal and transverse arches, thumb opposition, and the web space in the hand [10].

3. The Effect of HANDS Therapy

Shindo et al. [12] performed a randomized, controlled study among subacute patients (time from stroke onset within 60 days) with hemiparesis following stroke. They explored the effectiveness of HANDS therapy added to conventional rehabilitation as compared with splint therapy in addition to standard inpatient rehabilitation treatment for patients who could not fully extend their paretic fingers and could not perform pinch and release in their daily life, in a randomized, controlled trial design. Compared with the control group, the HANDS group showed significantly greater gains in the distal (hand/wrist) part of the Fugl-Myer Assessment (FMA) [13] and improvement of the Action Research Arm Test [14]. HANDS therapy is an intervention that resulted in improved hand function following stroke, while a systematic review [3] showed that none of the interventions identified showed a consistent pattern of improvement in hand function.

HANDS therapy improved upper extremity function even in patients with chronic stroke [7, 8]. Fujwara et al. [8] applied HANDS therapy to 61 patients with chronic hemiparetic stroke. Their mean time since stroke onset was 28.4 months. Three weeks of HANDS therapy improved FMA, the motor activity log 14 (MAL) amount of use score [15], and the modified Ashworth scale (MAS) [16]. Improvement of the FMA, MAL, and MAS lasted for 3 months after the end of HANDS therapy. In the study of Fujiwara et al. [7], arm and finger functions were assessed with the Stroke Impairment Assessment Set (SIAS) motor function score [17]. They found that both arm and hand function had been improved by HANDS therapy, and these improvements were maintained until 3 months after the end of HANDS therapy. They also showed improved capability of the paretic hand in ADL.

These studies showed that HANDS therapy improved arm and hand motor functions, increased the amount of use of the paretic upper extremity in ADL, and reduced finger and wrist spasticity, not only in subacute, but also in chronic stroke. The mean FMA gains with HANDS therapy were 12.2 in subacute patients [12] and 7.7 in chronic patients [8]. These gains surpassed the minimal clinically important difference for treatment-induced gains of 4.25 on the FMA [18].

4. The Mechanism of Functional Recovery and Neural Plasticity Induced with HANDS Therapy

Dose-dependent, task-specific, and use-dependent plasticity are principles of rehabilitation for functional recovery.

HANDS therapy improved motor function and increased the amount of paretic hand use. These improvements were maintained until 3 months after the end of HANDS therapy. These long-lasting effects of HANDS therapy can be explained by the concept of the threshold of effective rehabilitation, which was proposed by Han et al. [19]. If spontaneous arm use is above a certain threshold, then training can be stopped, as repeated spontaneous use provides a form of motor learning that further improves performance and spontaneous use. Below this threshold, training is in vain, and compensatory movements with the less affected hand are reinforced. In HANDS therapy, participants were trained to use their paretic hand for 8 hours in 3 weeks using closed-loop EMG-controlled NMES and a hand splint. Such an amount of training may be above the threshold of effective rehabilitation.

The effect of training is task-specific [20]. The aim of HANDS therapy is to make the paretic hand useful for ADL and to have the paretic hand participate in ADL. The key functions of the hand in ADL are grip and release and pinch and release. It is difficult for patients with moderate or severe hemiparesis to extend their fingers. The closed-loop EMG-controlled NMES, therefore, helps to extend the paretic fingers, and the splint helps the patient pinch and hold the objects with paretic fingers. Using this HANDS system, participants were trained to use their paretic hand in their ADL, producing proximal and distal coordinated movements, such as reach, grip and release, and pinch and release.

One of the mechanisms of functional recovery of stroke is use-dependent plasticity. Functional recovery involves changes in neuronal excitability that alter the brain's representation of motor and sensory functions. The inhibitory neurotransmitter GABA is critical for cortical plasticity. In animal studies, reducing $GABA_A$ergic inhibition proved beneficial for functional recovery [21, 22]. In humans, this $GABA_A$ergic inhibitory system can be assessed with a paired-pulse transcranial magnetic stimulation (TMS) technique, in which a conditioning TMS pulse below the threshold for eliciting a motor-evoked potential (MEP) inhibits a suprathreshold test stimulus at short intervals (1–5 ms) (short intracortical inhibition (SICI)) [23]. Fujiwara et al. [8] showed that HANDS therapy induced disinhibition of SICI in the affected hemisphere, and there was a direct correlation between the change of SICI in the affected hemisphere and the change of FMA. Patients who showed more disinhibition of SICI showed longer lasting improvement of motor impairment. It has been supposed that long-lasting functional reorganization of the brain may be mediated by disinhibition of intracortical inhibitory interneurons in severely hemiparetic patients. In moderate to severe hemiparesis, compensatory brain responses include increased activation in the surrounding damaged zone and masked network [24]. HANDS therapy strengthened disinhibition of the affected SICI. It is thought that compensatory disinhibition occurred in moderate to severe chronic stroke during functional recovery induced with HANDS therapy. The mechanism of functional recovery of the upper extremity is not able to be explained by the disinhibition of SICI alone. More is necessary to induce functional recovery.

HANDS therapy improved the spasticity of the fingers and wrist. Spasticity is often blamed for poor function in patients with minimal finger extension but some preservation of flexion [20]. The mechanisms underlying spasticity poststroke have not been fully elucidated, but decreased reciprocal inhibition may contribute to motor impairment in spastic hemiparesis [7]. In healthy subjects, group Ia-mediated reciprocal inhibition contributes to the suppression of antagonist muscle activity during movement [25, 26]. This reciprocal inhibition is disrupted among patients with spastic hemiparesis [7, 27]. HANDS therapy reduced cocontraction of finger flexors during finger extension movement. This may be due to the restoration of reciprocal inhibition with HANDS therapy. Fujiwara et al. [8] studied reciprocal inhibition with the flexor carpi radialis H reflex conditioning-test paradigm [28] before and after HANDS therapy. HANDS therapy increased the magnitude of presynaptic inhibition and long loop presynaptic inhibition. They found a significant correlation between restoration of RI and improvement of wrist spasticity.

Disinhibition of affected intracortical interneurons increases the activity of the descending projection from the affected hemisphere to the spinal cord. Increased activities of the descending projection to the spinal cord modulate the activities of reciprocal inhibitory interneurons [29, 30].

More evidence is needed to investigate the neural plasticity changes underlying functional improvement after HANDS therapy by using brain imaging techniques such as fMRI.

HANDS therapy was applied in subacute and chronic stroke patients. There was no report of adverse effects. We consider that HANDS therapy is suitable for subacute and chronic phase of stroke and patients with synergy level, who cannot extend their paretic finger enough to use their paretic hand in their ADL.

5. Conclusion

HANDS therapy is one of the neurorehabilitation therapeutic approaches that facilitates the use of the paretic upper extremity in daily life by combining closed-loop EMG-controlled NMES with a wrist splint. Functional recovery from stroke has been induced with HANDS therapy even in chronic and moderate to severe hemiparesis. The improvements of motor function and spasticity induced by HANDS therapy are based on cortical and spinal plastic changes.

As the other NMES, HANDS therapy may offer a promising option for the management of the paretic upper extremity in patients with stroke. Further development and clinical application of HANDS therapy are needed.

Competing Interests

There is no conflict of interests regarding the publication of this paper.

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Research Article

Cortical Reorganization in Patients Recovered from Bell's Palsy: An Orofacial and Finger Movements Task-State fMRI Study

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Objective. To explore cortical reorganization of patients recovered from Bell's palsy (BP) by task-state functional magnetic resonance imaging (fMRI) during finger and orofacial movements and provide more evidence for acupuncture clinical treatment of BP. *Methods.* We collected 17 BP patients with complete clinical recovery (BP group) and 20 healthy volunteers (control group) accepted the task-state fMRI scans with lip pursing movements and finger movements, respectively. *Results.* It was found that there were significant differences of brain functional status between the two groups. *Conclusions.* The results showed that there was cortical reorganization in the brain of patients recovered from BP after acupuncture treatment, which also suggested the relationship between the hand motor areas and facial motor areas of BP patients.

1. Introduction

Cortical reorganization, also called "cortical plasticity," is the ability of the cortex to adapt to changing circumstances and new information. Multiple studies demonstrated that functional plasticity occurred in various diseases, including brain lesions [1–3] and peripheral nerve lesions [4]. Bell's palsy is an acute, idiopathic, and unilateral paralysis of the face with a pure peripheral deafferentation and dysfunction of the facial nerve [5, 6], which is a common condition affecting approximately 20–35/100 000 people [7]. It is usually treated by medicine, surgical operation, acupuncture, and other clinical methods [8–11]. Previous studies have provided evidence that cortical reorganization played an important role in the recovery of Bell's palsy. For example, Rijntjes et al. used positron emission tomography (PET) and transcranial magnetic stimulation (TMS) to detect cortical reorganization in patients with facial palsy, which demonstrated that facial motor deafferentation leads to an enlargement and extension of the cortical hand field into the face area [12]. TMS was also used in facial paralysis with the task of tongue skills. The result showed the facial motor region was invaded by the neighboured tongue motor area bilaterally.

Functional magnetic resonance imaging (fMRI) is a popular radiological technique to investigate pathological mechanism in disease progression [13]. It has been used to detect patients with facial palsy recovery. Wu et al. [10] showed changed functional connectivity in the acute stage and subsequent reorganization during the recovery of the BP with resting fMRI. Hu et al. [14] found that increasing functional connectivity of the anterior cingulate cortex during the course of recovery from Bell's palsy might be related to the cortical reorganization.

BP is a disease of peripheral deafferentation and dysfunction of the facial nerve. It is a leading disorder of facial motor function. How does the cortical reorganization in facial motor area of patients recovered from BP and what is its relationship to hand motor area? With this aim, we detected cortical reorganization in recovery BP patients with two different motor tasks, the finger and lip pursing movements.

Table 1: Information of patients recovered from BP.

Number	Sex	Age	Paretic side	HBS (before treatment)	Duration (days)
mr76788	Female	39	Left	5	99
mr74727	Female	45	Left	5	38
mr79842	Female	42	Left	4	102
mr76789	Male	43	Right	3	38
mr79877	Male	48	Left	3	54
mr79577	Female	28	Right	4	35
mr81658	Female	28	Left	4	38
mr83703	Male	26	Right	4	77
mr93120	Male	26	Left	4	143
mr103930	Female	25	Right	4	273
mr93076	Male	49	Left	4	49
mr95181	Male	26	Right	3	43
mr102581	Male	30	Left	4	178
mr102582	Female	24	Right	3	68
mr102423	Female	44	Right	3	44
mr114175	Male	46	Left	3	146
mr111924	Female	27	Right	3	67

2. Materials and Methods

2.1. Subjects. All subjects recruited in this study were divided into two groups, recovered palsy group and healthy control group. The recovered palsy group was composed of 17 cases of patients recovered from BP (all right-handed, female 9, male 8, as shown in Table 1), who were the out-and-in patients from the First Affiliated Hospital of Anhui University of TCM (traditional Chinese medicine). They had been assessed as clinical recovery after acupuncture treatment by the House-Brackmann facial nerve grading system (HBS) (House and Brackmann, 1985) [15]. HBS has been mostly widely used in studies of peripheral facial nerve palsy in recent years. This scale ranges from 1, representing normal facial movements, to 6, representing no movements. The control group was composed of 20 healthy volunteers (female 7, male 13) from Anhui University of TCM and the hospital staff who were right-handed. All subjects were with no history of mental or neurological disease, with no obvious abnormality disorder or drug use, and with no obvious abnormality in brain structure. And, also, this study was approved by the Institutional Review Board of the First Affiliated Hospital of Anhui University of TCM, and written informed consent was obtained from each participant prior to the experiment.

2.2. Data Acquisition. The experiment was performed in the MRI room of the Medical Imaging Center, the First Affiliated Hospital of Anhui University of TCM. The Siemens Symphony 1.5 T MRI whole body scanner (Siemens Medical Systems, Germany) and standard head coil were used. Before experiment, the participants were requested to change clothes, rest, and then enter the scanning room after the whole body had been relaxed. They were instructed to lie down with eyes closed and to stay awake. All lights in the scanning room were turned off to avoid unwanted visual stimulation. We also should have expounded two task-state actions to the participants. During the entire scanning process, the subjects were asked to avoid psychological activity as far as possible.

Five sequences were scanned as follows: (1) pilot images; (2) T2-weighted images to rule out any disease of the brain; (3) EPI-BOLD; (4) T1-weighted 3D anatomical images: the sagittal position was taken, and total of 176 slices were scanned which covered the whole brain. The spoiled gradient echo sequence was used, with TR/TE/FA = 2100 ms/3.93 ms/13°, FOV of 250 × 250 mm, slice thickness/spacing = 1.0 mm/0.5 mm, and resolution of 256 × 256. (5) Task-state fMRI took about 30 minutes to complete all of the data acquisition.

Task-State fMRI. Lip pursing movements and finger movements were selected as two task-state actions. EPI-BOLD was used with TR/TE/FA = 3000 ms/30 ms/90°, slice thickness/spacing = 3.0 mm/0.75 mm, FOV 192 mm × 192 mm, and FOV 64 × 64 mm. And the data of task-state scanning used block design, every block took 30 seconds, and all scanning of data of task-state fMRI took 6 minutes, 120 cardinal numbers of functional data. Every functional data acquisition took 3 seconds (TR), as shown in Figure 1.

2.3. Data Preprocessing. Data analysis was performed using the software of AFNI (http://afni.nimh.nih.gov/afni/) in the Laboratory of Digital Medical Imaging, the First Affiliated Hospital of Anhui University of TCM. Initially, the first 4 time points of the functional images were discarded to avoid the instability of the initial MRI signal and the remaining images were realigned to the first volume. Thereafter, the images were normalized to the standard Talairach atlas and then smoothed spatially using a 6 mm full width at half maximum (FWHM) Gaussian kernel to decrease spatial noise. The time

Table 2: Intergroup analysis of areas when making finger movements.

Region	Side	Talairach (mm)			Z	Voxels
		x	y	z		
PCC	Right	−1.5	49.5	11.5	1.211	369
Precuneus	Left	1.5	76.5	32.5	1.507	353
Transverse temporal gyrus	Left	61.5	16.5	11.5	0.892	186
SI/MI	Right	−61.5	22.5	14.5	0.859	92
Middle temporal gyrus	Right	−64.5	16.5	−6.5	0.661	83
CMA	Left	1.5	19.5	41.5	0.562	80
Parahippocampal gyrus	Right	−19.5	1.5	−9.5	−0.733	71

The threshold was set at $P = 0.05$, $\alpha < 0.05$, cluster = 61 (corrected with Monte-Carlo method). PCC: posterior cingulate cortex; MI: primary motor cortex; SI: primary somatosensory cortex; CMA: cingulate motor area.

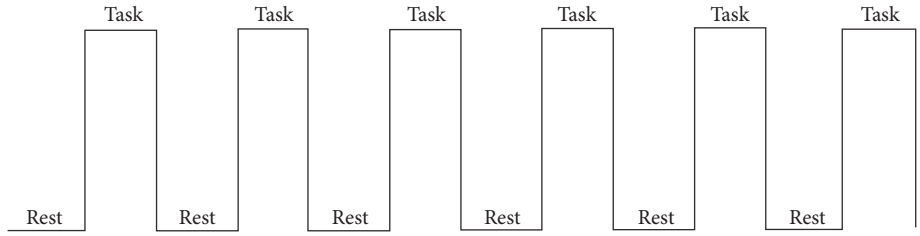

Figure 1

series from each voxel was detrended using the method of linear least squares to remove low-frequency noise and signal drift. For each subject, the preprocessed fMRI data were then submitted for analyses using the general linear model, and the *coef* value in the individual analysis results was extracted as the contrast image for further analysis. Before processing, individual data of right-sided facial palsy patients were flipped along y-axis so that all data could be processed unilaterally.

2.4. Intergroup Analysis. Before intergroup analysis, the individual data with head movements more than 2 mm or 2° were excluded to avoid the possible influence of head movements on the results of the data analysis. As a result, 4 cases in the palsy recovered group were excluded. Intergroup comparison was performed with 3dttest++ to investigate the variation of brain activation between patients and controls. The results of intergroup analysis were corrected using Monte-Carlo simulation, with $P = 0.05$, $\alpha < 0.05$, cluster = 61. To detect the cortical functional reorganization in patients with facial paralysis, the regions of interest were extracted from the statistic activation maps from hand task experiment for controls and mouth task experiment for patients to get the intersection.

3. Results

3.1. General Information. 17 cases of BP group (mean age: 35.06 years, range: 20–70 years) and 20 cases of healthy control group (mean age: 31.7 years, range: 20–70 years) were not significantly different among subjects' age distributing and the sample size of two groups. To address the significant differences in cortical reorganization between different groups, the results of group analysis for each group were showed as follows. There were no subjects removed from data analysis. In the study, the data of right-sided BP patients were flipped along the y-axis so that all data could be processed unilaterally. So all patients can be considered the left-sided BP patients. The left activated areas were considered to be contralateral, and the right activated areas were ipsilateral.

3.2. Finger Movements Task-State. As shown in Table 2 and Figure 2, when performing finger movements compared with the healthy control group, it showed increased activation in the contralateral PCC (posterior cingulate cortex), MI (primary motor cortex), SI (primary somatosensory cortex), middle temporal gyrus and ipsilateral CMA (cingulate motor area), precuneus, and transverse temporal gyrus. There was decreased signal in the contralateral parahippocampal gyrus (Table 2, Figure 2).

3.3. Lip Pursing Movements Task-State. When making lip pursing movements compared with the healthy control group, it showed decreased activation in the ipsilateral culmen, CMA (posterior cingulate cortex), transverse temporal gyrus, SI (primary somatosensory cortex), precuneus, and contralateral superior occipital gyrus with lip pursing movements (Table 3, Figure 3).

4. Discussion

This is a report on the changes in the brain functional status of patients recovered from BP by movements task-state functional MRI, which would provide more evidence for clinical treatment. With this objective, differences of

Table 3: Intergroup analysis of areas when making lip pursing movements.

Region	Side	Talairach (mm)			Z	Voxels
		x	y	z		
Culmen	Left	37.5	55.5	−24.5	−1.703	621
PCC	Left	1.5	40.5	17.5	−0.837	154
Transverse Temporal Gyrus/SI	Left	61.5	13.5	11.5	−1.342	121
Superior Occipital Gyrus	Right	−31.5	82.5	23.5	−0.832	110
Precuneus	Left	19.5	70.5	44.5	−0.780	86

The threshold was set at $P = 0.05$, $\alpha < 0.05$, cluster = 61 (corrected with Monte-Carlo method). BA: Brodmann area; PCC: posterior cingulate cortex; SI: primary somatosensory cortex.

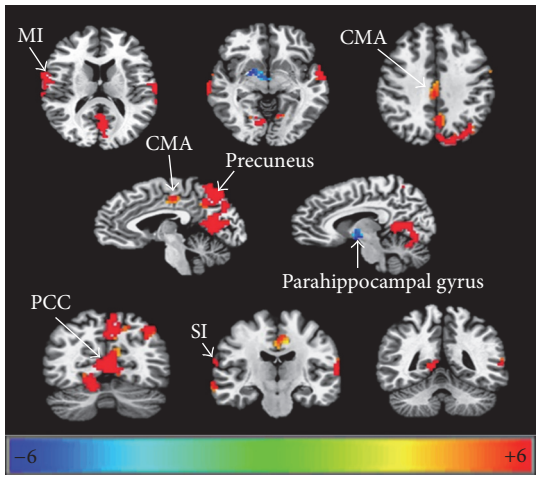

Figure 2: Cortical reorganization in the areas of palsy recovered group compared to healthy control group when conducting finger movements. $P = 0.05$, $\alpha < 0.05$, corrected with Monte-Carlo method. PCC: posterior cingulate cortex; MI, primary motor cortex; SI: primary somatosensory cortex; CMA: cingulate motor area.

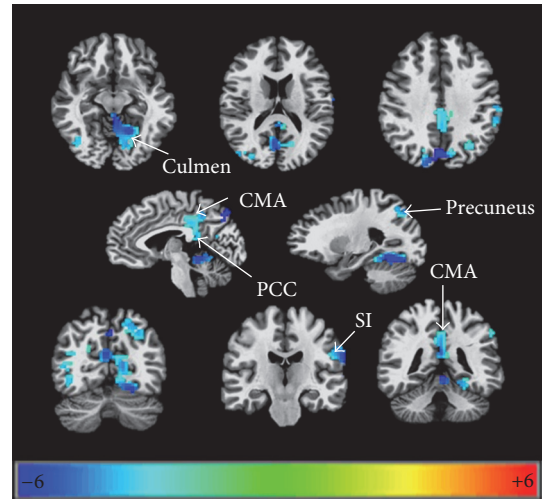

Figure 3: Cortical reorganization in the areas of palsy recovered group compared to healthy control group when conducting lip pursing movements. $P = 0.05$, $\alpha < 0.05$, corrected with Monte-Carlo method. PCC: posterior cingulate cortex; SI: primary somatosensory cortex.

brain functional status between the recovered palsy group and healthy control group were investigated in this study. Firstly, we would discuss two important questions, whether cortical reorganization existed or not and what cortical reorganization might imply.

4.1. Cortical Reorganization in Patients Recovered from BP. From results of this paper, it showed that there were significant differences of cortical function status between recovered palsy group and healthy control group during finger movements and lip pursing movements. Therefore, we could get the conclusion that cortical reorganization still existed in patients recovered from BP, or the brain functional status had not returned to the condition before the disease. Bell's palsy patients had been assessed as recovery when their grade of HBS was I; it just implied the clinical symptoms disappeared, but it did not mean cortical reorganization would return to status before the disease. Actually, previous studies have indicated that cortical reorganization in multiple related sensorimotor areas existed during the whole pathological stage of BP [10, 14, 16]. This study indicated cortical reorganization existed in the early recovery stage. In general, patients will stop treatment after clinical symptoms disappear. This study also implied that perhaps patients should continue the treatment even after clinical recovery to enhance the thorough recovery of brain function.

4.2. Differences between Recovered Palsy Group and Healthy Control Group. In this study, significantly increased activation in posterior cingulate cortex (PCC), primary somatosensory cortex (SI), primary motor cortex (MI), and cingulate motor area (CMA) and decreased activation in parahippocampal gyrus during finger movements were found. And we also observed decreased signal in primary somatosensory cortex (SI), posterior cingulate cortex (PCC), precuneus and culmen during lip pursing movements. These activated areas, which were associated with hand and orofacial movements, were components of a network that controlled the cortical and subcortical representation of voluntary facial movements, which were reported in many studies [15, 17, 18]. The functional network of the human brain was pretty complicated, especially in the way in which these regions interact [19]. Posterior cingulate cortex (PCC), precuneus,

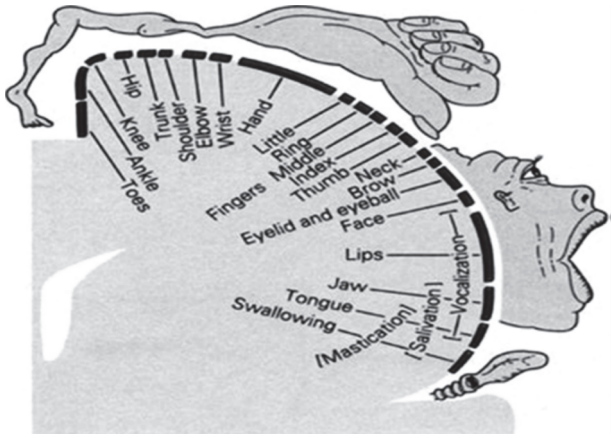

Figure 4: Penfield and Rasmussen's homunculus.

and parahippocampal gyrus are known to be related to the brain's default mode network (DMN), which is defined as a set of regions that is spontaneously active during passive moments [20] and associated with affective processing, memory, and self-projective thinking [21]. There was also a study reporting that Bell's palsy would bring patients negative emotion [22]. It might be the reason for activated DMN. Culmen is one part of the cerebellum which plays an important role in the motor control. It may also be involved in some cognitive function such as attention and language and in regulating fear and pleasure responses [14, 23]. There was a study reported that cerebellum was activated during functional recovery from transient peripheral motor paralysis, which was in accordance with our results [18].

Another remarkable characteristic of the results is that the decreased activation of fMRI as conducting lip pursing movements mainly located on the ipsilateral to the paretic side; it may be due to compensatory mechanism of brain function. However, the increased activation with finger movements located on the bilateral cerebral hemispheres. Contralateral SI and MI were activated with finger movements. A task-state fMRI study during facial and mouth movements also found activated areas were contralateral to the facial palsy even after clinical recovery [15]. It was explained by the brain's reaction to the failure of facial muscle movement. It can suggest that facial function has not completely recovered whereas the clinical assessment did not show an impairment of facial movements.

4.3. Relationship of Hand Motor Area and Facial Motor Area. It was also detected there were increased activation during finger movements and decreased activation during lip pursing movements, which demonstrated that cerebral blood flow in facial motor area of patients recovered from BP was reduced, while cerebral blood flow in hand motor area of patients was enhanced compared to healthy volunteers. Locations of hand and facial representation areas are neighbouring in the primary motor cortex (Figure 4). There were many studies reporting cortical reorganization of these two neighbouring areas. For example, Florence et al. [24] reported that, in the somatosensory thalamus and cortex of monkeys after accidental forelimb amputations, the forelimb representation in the ventroposterior nucleus became completely reactivated by intact inputs from the stump of the arm and from the face. Cohen et al. [25] also used functional magnetic resonance imaging to study brain activity to vibratory stimulation and voluntary movements of body parts above and below the lesion and found that no response to vibratory stimulation of the hand was observed in the primary somatosensory cortex (SI) hand area, which was conversely recruited during tongue movements that normally evoke responses only in the more lateral face area, which suggested the activated hand representation area had extended facial motor area. In studies of Bell's palsy, Rijntjes et al. [12] also found that patients with facial palsy activated a larger part of the cortex than normal volunteers when making fractionated finger movements, as measured with PET and TMS. It inferred that hand representation area extended into the orofacial area. It was mostly corresponding to our results. It might be the reason for distal end points which were used to acupuncture treatment. Not only have points located on the face been used, but also points, such as Hegu (L14), which is located on the hand, have been used in acupuncture treatment for Bell's palsy.

5. Limitation of This Study

Our results indicated that cortical reorganization existed in the early recovery stage of BP. The evidence provided in this research for the relationship of cortical reorganization with acupuncture treatment is limited. Therefore, we cannot exclude the possibility that the results might just reflect the self-recovery of Bell's palsy. This study tried to light the underlying mechanism of recovery of BP, although further researches are still needed. Although considering the probability that severity of BP in acute phase and duration might have an influence on the cortical reorganization, there was no abundant data to analyze their relationship. This valuable research will be carried out after we collected enough data.

6. Conclusions and Perspective

We have concluded evidence that functional status in the brain of patients recovered from Bell's palsy differed from those in healthy control group when making finger movements and lip pursing movements. The changed activation between the two groups included motor association cortex and cerebellum. All of these changes in the cortex might be relevant to the differences in the brain functional status. Therefore, we propose that cortical reorganization continued at different pathological stages in patients with Bell's palsy besides recovered stage. And further evidence was still needed to support our proposition.

Competing Interests

The authors declare that there are no competing interests regarding the publication of this paper.

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Research Article

Merging and Fractionation of Muscle Synergy Indicate the Recovery Process in Patients with Hemiplegia: The First Study of Patients after Subacute Stroke

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Loss of motor coordination is one of the main problems for patients after stroke. Muscle synergy is widely accepted as an indicator of motor coordination. Recently, the characteristics of muscle synergy were quantitatively evaluated using nonnegative matrix factorization (NNMF) with surface electromyography. Previous studies have identified that the number and structure of synergies were associated with motor function in patients after stroke. However, most of these studies had a cross-sectional design, and the changes in muscle synergy during recovery process are not clear. In present study, two consecutive measurements were conducted for subacute patients after stroke and the change of number and structure of muscle synergies during gait were determined using NNMF. Results showed that functional change did not rely on number of synergies in patients after subacute stroke. However, the extent of merging of the synergies was negatively associated with an increase in muscle strength and the range of angle at ankle joint. Our results suggest that the neural changes represented by NNMF were related to the longitudinal change of function and gait pattern and that the merging of synergy is an important marker in patients after subacute stroke.

1. Introduction

Motor dysfunction due to neural disorders is responsible for several complications in patients recovering from stroke [1]. In particular, gait disorders can affect the patient's ability to participate in daily activities [2]. Impairments resulting in gait disorder have been reported previously, such as muscle weakness [3], spasticity [4], and, most importantly, poor motor coordination [5].

Previous studies have investigated the problem of motor coordination using cocontraction between agonist and antagonist muscles in patients after stroke [5–7]. However, the effects of cocontraction on gait were not consistent in these studies. One study suggested that excessive cocontraction during gait may adversely affect the energy cost during gait [7], whereas another study reported that cocontraction is needed as an adaptive behavior for retaining stability during gait [5]. This inconsistency in evidence reflects the limitations of using cocontraction as an indicator of motor coordination during gait. Therefore, a more comprehensive and specific indicator is needed for motor coordination in patients after stroke.

In general, the brain needs to coordinate the degrees of freedom in the musculoskeletal system during movement [8],

and muscle synergy is hypothesized to manage the problem with degrees of freedom [9]. Based on this hypothesis, the central nervous system controls muscle synergy, which comprehensively coordinates the activation of several muscles during movement. Recent studies have demonstrated that the number and structure of muscle synergies can be directly identified using nonnegative matrix factorization (NNMF) with surface electromyography (EMG) during gait and reaching tasks [10–12]. The physiological validity and robustness of this method have been demonstrated in previous studies [13, 14].

Using this method, it was reported that the number of synergies did not change in patients with spinal cord injury (SCI) [15]. However, the evidence is conflicting in poststroke patients, with one study demonstrating a similar number of synergies in poststroke patients and healthy adults [16] and another reporting a decreased number of synergies in patients after stroke [17]. These contradictory results may be caused by differences in the duration after stroke. The study that reported no changes in the number of synergies recruited patients after subacute stroke [16], whereas the study demonstrating a reduced number of synergies recruited patients after chronic stroke [17]. Furthermore, one previous study investigated the change in muscle synergy in patients after chronic stroke [18]. The study demonstrated that muscle synergies were fine-tuned and that the number of synergies was increased in some patients with improved motor function. However, the change in muscle synergies, including the number and structure of synergies, in patients after subacute stroke has not been clarified.

Of clinical importance is another previous study that demonstrated that muscle synergy calculated by NNMF was strongly associated with a dynamic response during movement [19]. For stroke patients, abnormal gait patterns were often represented by gait kinematics and kinetics. For example, abnormal gait kinematics were mostly represented at the knee joint or ankle joint [20], whereas the change in gait kinetics relating to gait function was shown at the ankle joint [21]. However, the longitudinal relationship between muscle synergy and gait dynamics in stroke patients is unknown.

Another study reported that the merging and fractionation of muscle synergies could explain the changes in the number of synergies in patients after stroke [22]. The degrees of merging and fractionation were individually associated with the characteristics of patients. Merging was related to impairment of the upper limbs, and fractionation was related to the duration after stroke. Thus, it is considered that merging and fractionation could be used as indicators of motor coordination in patients after stroke. However, the mechanism of how these changes occurred and whether they are related to the recovery of motor function remain unclear.

Furthermore, most results regarding muscle synergy were demonstrated by cross-sectional studies. However, longitudinal changes in muscle synergy are still unknown. We conducted two consecutive measurements and clarified the changes in the number and structure of muscle synergies in patients after subacute stroke and investigated the relationship between the change in muscle synergy and change in motor function or gait dynamics during the recovery process.

Table 1: General characteristics of stroke patients.

	$N = 13$
Sex (M/F)	10/3
Age (years) [range]	58.8 ± 13.2 [30–82]
Height (cm)	160.2 ± 7.3
Weight (kg)	65.4 ± 11.7
Brunnstrom stage (V/VI)	(11/2)
Duration after stroke (day) [range]	66.8 ± 24.2 [38–118]
Barthel index [range]	86.5 ± 9.9 [65–95]
Gait speed (m/sec) [range]	0.54 ± 0.24 [0.50–1.38]

M: male; F: female.
Data are expressed as mean ± SD and range for stroke patients.

2. Materials and Methods

2.1. Participants. This study was conducted at the Yufuin Kosei Nenkin Hospital in Oita, Japan. Patients with the following inclusion criteria were recruited: (1) a single stroke within 6 months prior to the study; (2) ability to walk independently using an ankle-foot orthosis or T-cane; (3) no gait symptoms from Parkinson's or ataxia; (4) no pain during gait due to orthopedic disease; (5) no limitation of activity due to heart disease; and (6) no difficulty in understanding the experimental tasks due to cognitive problems. Thirteen patients who had experienced subacute stroke met the inclusion criteria and participated in this study (mean time elapsed after stroke: 66.8 ± 24.2 days). The patients' clinical characteristics are presented in Table 1. This study was approved by the Ethics Committee of Kyoto University Graduate School, Faculty of Medicine, and Yufuin Kosei Nenkin Hospital, and we obtained informed consent from all patients.

2.2. Experimental Protocol and EMG Recordings. Two measurements (first and second measurements) were performed at 1-month intervals. Between the first and second measurements, all patients participated in the inpatient rehabilitation program, which included gait training, balance training, and task-specific training for activities of daily living (ADL) for 60 minutes per day, five times per week. During each recording, gait measurements and clinical measurements were performed. For the gait measurement, two gait trials were performed by asking patients to walk a 10 m long walkway at a chosen speed with or without a cane. Muscle activity was recorded simultaneously with surface EMG (sEMG) using a Trigno Wireless System (Delsys Co., Boston, USA; sampling rate: 4000 Hz), which also recorded the data from a 3D accelerometer (ACC). The sEMG activity was recorded from the tibialis anterior (TA), lateral gastrocnemius (GS), soleus (SL), gluteus medius (GM), rectus femoris (RF), vastus medialis (VM), biceps femoris (BF), and semitendinosus (ST) muscles of the affected side, and another sensor was placed on the heel of the measured limb to record the ACC data.

The corrected sEMG data were bandpass-filtered (20–250 Hz), rectified, and then low-pass filtered (10 Hz). Each gait cycle was determined by ACC data and normalized to 200 data points. Furthermore, the amplitude was normalized

to the peak activity recorded during five gait cycles. A factor analysis was performed with the normalized data (nEMG).

2.3. Muscle Synergy Extraction. For each subject, the nEMG data were separated into patterns of synergies and muscle weightings using an NNMF algorithm [12]. The nEMG data $m(t)$ are represented by the following equation:

$$m(t) = \sum_{i-1}^{n} C_i(t) W_i. \quad (1)$$

This algorithm could reveal synergies in the following two matrices: $C_i(t)$, which denotes the activation pattern of each synergy during five gait cycles ($n \times t$ matrix; n = number of synergies, t = time point), and W_i, which represents the weightings of the muscles involved in each synergy ($m \times n$ matrix; m = eight muscles of the paretic leg). The NNMF algorithm was initialized with two random matrices of activation patterns and weightings. The nEMG data were reconstructed by iteratively updating the values of these matrices until they converged.

2.4. Determining the Number of Synergies for Each Subject and Group. The NNMF analyses were performed with the output restricted to one, two, three, four, or five synergies, with no a priori assumptions about the adequate number of synergies. The reconstructed EMG (rEMG) was calculated by performing matrix multiplication, with both matrices indicating the activation pattern and weightings of synergies; the sum of squared errors (nEMG-rEMG) was then calculated. The variability accounted for (VAF), which was the ratio of the sum of the squared error to the sum of the squared nEMG, was calculated to determine whether the minimum number of synergies corresponded with adequate rEMG. Because the threshold of VAF could potentially change the number of synergies, we used the threshold from a previous study [17]. We determined that additional synergies were not required if VAF including all muscles was ≥90%.

2.5. Merging and Fractionation Indices. The change in structure of muscle synergy was investigated using merging and fractionation indices calculated with a linear combination, as reported in a previous study [22]. The merging index was defined as the ratio of the frequency of merging of the synergy to the total number of synergies in the first measurement, whereas the fractionation index was defined as the ratio of frequency of fractionation of the synergy to the total number of synergies in the first measurement (Figure 1).

2.6. Clinical Measures. The gait speed of each patient was measured using a stopwatch. The Timed Up and Go test (TUG) and the Short-Form Berg Balance Scale (SFBBS) were used to assess the function of dynamic or static balance for each patient. The Barthel index (BI) was measured as a functional outcome of ADL. Furthermore, the muscle strength (N·m) of five muscles (hip flexor, knee extensor, knee flexor, ankle dorsiflexor, and ankle plantar flexor) was measured using a hand-held dynamometer (μ-tas F-1; ANIMA Corp., Tokyo, Japan) and normalized by weight (N·m/kg). The sum of the five muscle strengths represented the parameter for all the muscles. Furthermore, the change in the parameters of motor function (Δ speed, Δ TUG, Δ SFBBS, Δ BI, and Δ strength) was represented by the ratio of change among trials involving the value of the first measurement.

Table 2: Determined peak position during gait cycle at three joints.

Parameters	Joint	Peak motion	Range (% gait cycle)	
			From	To
HF1	Hip	Flexion	0	20
HE		Extension	0	100
HF2		Flexion	90	100
KF1	Knee	Flexion	0	20
KE		Extension	20	50
KF2		Flexion	50	100
AP1	Ankle	Planter flexion	0	20
AD		Dorsiflexion	0	100
AP2		Planter flexion	50	70

2.7. Kinematical Measures. A follow-up gait measurement was also performed in the same motion analysis laboratory. The laboratory had a 3D motion analysis system (T-10; Vicon Motion System Ltd., Oxford, UK) with eight cameras and a sampling frequency of 100 Hz. Reflective markers were attached to the body according to the Vicon Plug-in-Gait (PiG) marker placement protocol (full body). Data were processed using PiG software, which uses a Woltring filter, and joint kinematics were generated using inverse dynamics analysis within Nexus version 1.7 software (Vicon Motion System Ltd.). The data recorded by 3D motion analysis were time-normalized to 100% gait cycle (GC). The parameters of gait kinematics at the hip, knee, and ankle joints were detected as the peak of the joint angle during the gait cycle, as shown in Table 2. Furthermore, the changes in gait kinematics between measurements were calculated as the difference or ratio of change in peak or angle range, respectively.

2.8. Statistical Analyses. First, interclass correlation coefficients ($ICC_{(1,1)}$) were calculated between the two trials of the first measurements to investigate the test-retest reliability of the number of synergies indicated by NNMF. Second, the paired t-test and Wilcoxon signed-rank test were used to examine the differences in clinical parameters, gait kinematics, and the number of synergies between the two measurements. Furthermore, the relationship between the merging index or fractionation index and the change in clinical parameters or gait kinematics was investigated using multiple linear regression with stepwise procedures and using the change in clinical parameters and gait kinematics at three joints as explanatory variables and the merging and fractionation indices as target variables.

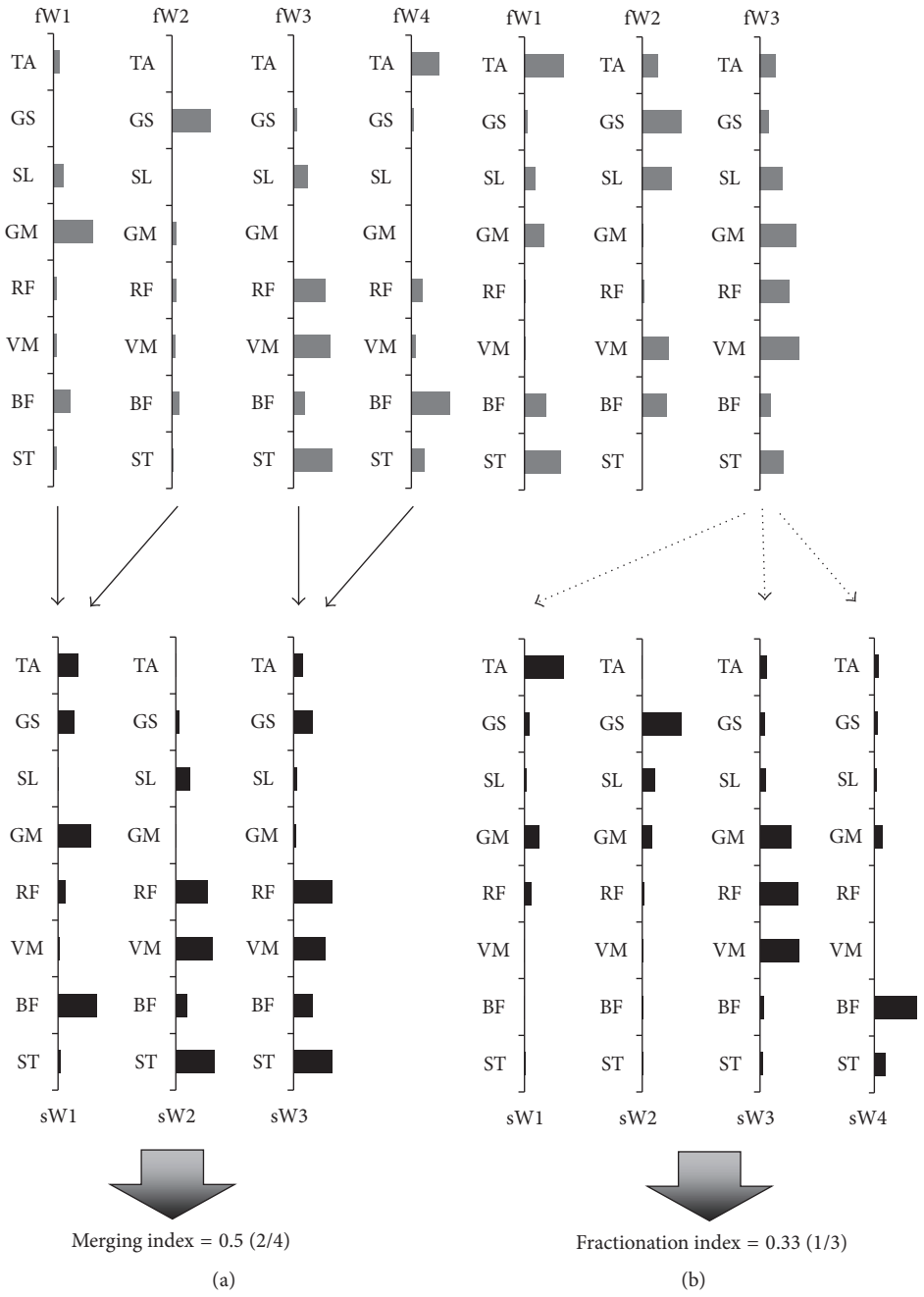

Figure 1: Merging and fractionation of the synergies. The figures show the merging (solid line) and fractionation (dotted line) of the synergies at the first (gray) and second measurements (black). (a) Merging of synergies recorded from a patient; the weighting of the sW2 and sW3 synergy was reconstructed by linearly combining two pairs of synergies (fW1 and fW2, fW3 and fW4) from the first measurement. (b) Fractionation of the synergies that were recorded; the weighting of the fW3 synergy at the first measurement was reconstructed by linearly combining three synergies (sW1, sW3, and sW4) from the second measurement.

3. Results

3.1. Validity of the Number of Synergies. Table 3 shows the changes in the number of synergies, merging and fractionation indices, and the motor function at the first measurement. Regarding the number of synergies, the results showed high test-retest reliability (ICC = 0.81, almost perfect).

3.2. Change in the Motor Function and Number of Muscle Synergies. Furthermore, the results showed that gait speed and muscle strength had significantly improved ($p < 0.01$ and $p < 0.05$, resp.). Other parameters including BI, TUG, and BBS also significantly improved. However, no consistent changes in the number of synergies between the first and second measurements were found ($p = 0.73$).

Table 3: Affected side, synergy information, and clinical status.

Patients	Affected side	Duration after stroke (days)	Synergy number at first measurement	Synergy number at second measurement	Merging index	Fractionation index	Gait speed	Barthel index	BRSs
1	L	65	2	2	0.00	0.50	0.50	85	4
2	L	69	2	2	0.00	0.00	0.54	95	5
3	L	46	2	3	0.00	1.00	0.86	90	5
4	R	45	3	3	0.00	0.000	0.51	85	5
5	R	62	3	4	0.00	1.00	0.85	95	5
6	L	46	3	4	0.33	1.00	0.62	65	5
7	L	115	3	3	0.33	0.33	0.99	90	6
8	L	80	3	3	0.33	0.00	0.80	95	5
9	R	74	3	4	0.67	0.33	1.10	90	5
10	L	118	4	3	0.50	0.25	1.38	95	6
11	L	56	5	5	0.80	0.40	0.73	90	5
12	L	55	5	3	0.60	0.40	0.69	85	5
13	R	38	5	3	0.60	0.20	0.93	65	5

L: left; R: right.

Table 4: Results of multiple linear regression analysis of gait kinematics.

(a)

Merging index (y)	Model R^2	Predictors (x)	β	95% CI	p
Model 1: strength	0.427	Intercept			<0.01
		Strength	−0.651	−1.47, −0.19	<0.05
Model 2: strength/range of ankle	0.647	Intercept			<0.01
		Strength	−0.558	−1.26, −0.17	<0.05
		Range of ankle	−0.481	−1.16, −0.07	<0.05

(b)

Fractionation index (y)	Model R^2	Predictor (x)	β	95% CI	p
Model 1: BI	0.333	Intercept			<0.05
		BI	0.577	0.15, 4.84	<0.05

In addition, the kinematics did not show a significant change between two measurements. The peaks of flexion at the hip (hip F1) and knee (knee F1, F2) tended to increase after a month; however, the other peak angles at the three joints did not show a consistent change between two measurements. Furthermore, the ranges of hip and knee joints had increased since the first measurement; however, the ankle joint range did not show a consistent change.

3.3. Relationship between the Changes in Muscle Synergy and Motor Function or Gait Kinematics. Merging of synergy was observed in eight patients (61.5%) after stroke, whereas fractionation was found in 10 patients (76.9%) after stroke. The merging index was associated with the change of muscle strength and range of the ankle joint with a significant coefficient of determination (Table 4). However, the fractionation index was significantly related to only the improvement in BI. Changes in gait speed, SFBBS, and TUG were not significantly associated with the merging or fractionation indices.

4. Discussion

Our present study clarified the longitudinal change in muscle synergy calculated using NNMF for patients after subacute stroke. The high test-retest reliability was confirmed by the number of synergies calculated by NNMF. Using this method, a consistent change in the number of synergies was not found at monthly measurements, even though patients had significantly improved gait speed. However, merging of synergy was found in 61.5% of patients and fractionation of synergy was found in 76.9% of patients in this study. Furthermore, the extent of merging and fractionation depended on motor function and gait dynamics.

A previous study showed a change in timing and composition of muscle synergy in chronic stroke patients [18]. The results showed that the fine-tuning of muscle synergy and the increase in the number of synergies were associated with improvement in motor function. However, in this study, a consistent increase or decrease of the number of synergies was not found in subacute stroke patients with improved motor function. The results reflected that the neural networks relating to the number of synergies in subacute stroke patients did not change homogeneously.

In a previous cross-sectional study, severe stroke patients showed higher merging index and lower motor function as estimated by the Fugl-Meyer scale [22]. As a longitudinal change in present study, the present results suggest that higher merging index was associated with poor improvement of outcome, such as muscle strength and gait kinematics.

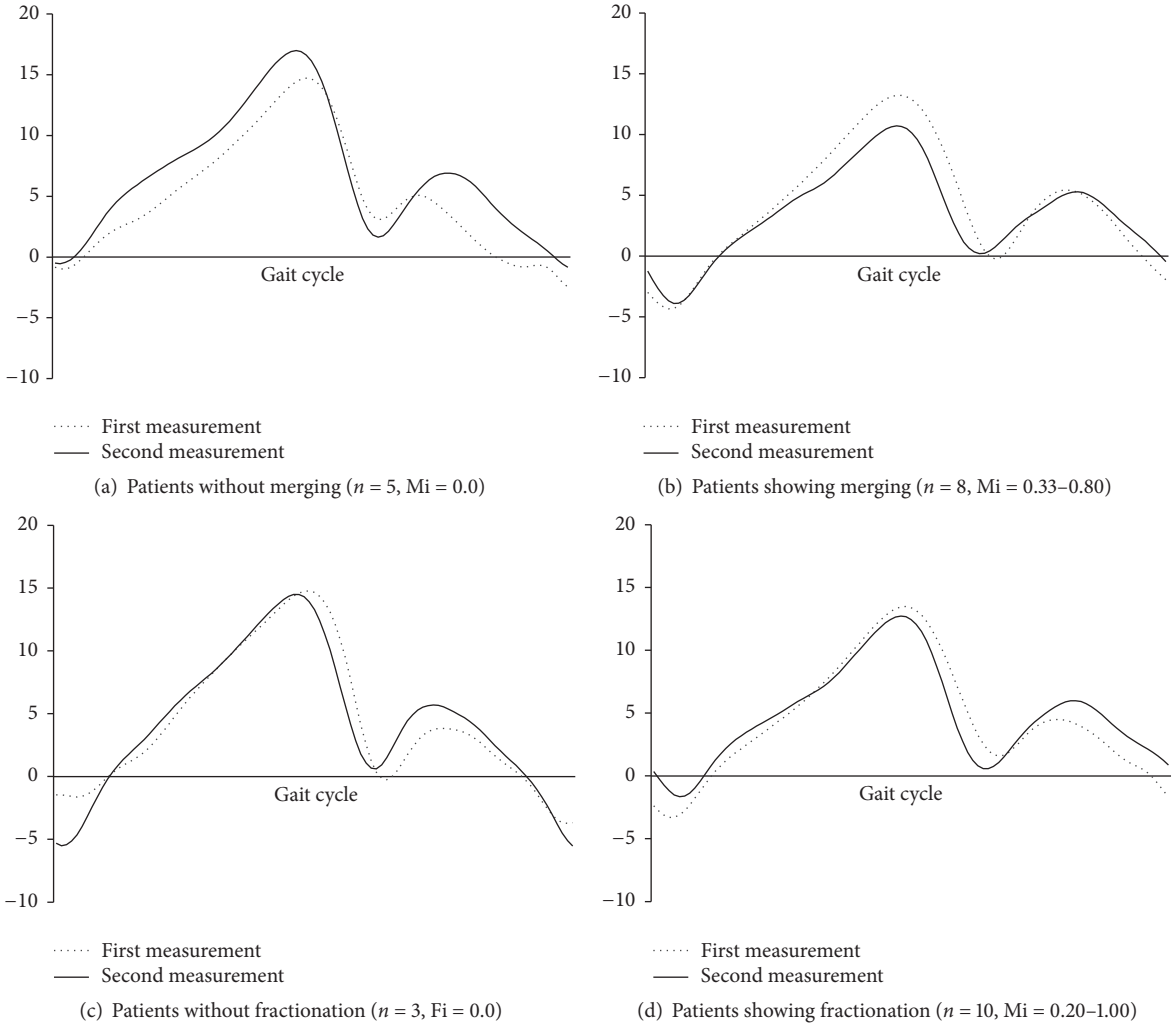

Figure 2: The change of ankle joint angle. The group with merging (b) showed limitation in the range of the ankle joint angle. The patients who did not show merging (a) had the same joint angle range. The group without or with fractionation (c and d) did not show the consistent change of gait kinematics.

Specifically, the patients with merging of synergy had poor improvement in muscle strength and restriction of ankle joint range at monthly measurements (Figure 2). The merging of synergy indicated by NNMF is thought to represent synchronization of the neural network. Therefore, it is considered that the merging of synergy may represent the compensative neural change to achieve a dynamic response after improvement of gait.

The fractionation index was associated with duration after stroke in a previous study [22]. In the present study, an association between the fractionation and duration after stroke was not found because the patients were inpatients. However, the fractionation index was related to the improvement in ADL. This suggested that the fractionation of synergy was influenced by the complexity of several movements in ADL during the recovery process. However, the mechanism of fractionation of synergy is not clear. Future studies are needed to investigate the background of fractionation of synergy.

The present study had some limitations. First, our sample size was small for the convenience of sampling, resulting in a small range of variability of motor function in the subjects. Future studies should include patients with more severe symptoms to allow a better understanding of the characteristics of synergy behavior. Other limitations were the small number of gait cycles assessed and use of a cane by some patients. These methodologies could affect the extraction of muscle synergies. However, a previous study also used a small number of gait cycles (10 gait cycles) for patients with SCI who were unable to walk long distances. Thus, a larger number of gait cycles and gait measurements without a cane are required to accurately investigate the synergy during gait. Furthermore our results showed the neural change during the short period, in which the patients significantly improved motor function. These results could not demonstrate the full recovery process in patients after stroke. Therefore, future studies should also measure the muscle synergy and motor function at more time

points to clarify the long-term changes in muscle synergy in patients after stroke.

5. Conclusion

The results of this study showed that the number of synergies did not consistently change with the recovery of motor function in subacute stroke patients. The merging and fractionation of the synergies during gait occurred depending on motor function. The merging of synergy was especially related to the unchanged muscle strength and abnormal gait pattern. The results of the present study suggest that NNMF can be used to clarify the characteristics of motor coordination in stroke patients and that the merging of synergies is thought to be an important marker of poor motor coordination.

Competing Interests

The authors declare no conflict of interests with respect to the authorship and publication of this article.

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Research Article

Pain Induced during Both the Acquisition and Retention Phases of Locomotor Adaptation Does Not Interfere with Improvements in Motor Performance

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Cutaneous pain experienced during locomotor training was previously reported to interfere with retention assessed in pain-free conditions. To determine whether this interference reflects consolidation deficits or a difficulty to transfer motor skills acquired in the presence of pain to a pain-free context, this study evaluated the effect of pain induced during both the acquisition and retention phases of locomotor learning. Healthy participants performed a locomotor adaptation task (robotized orthosis perturbing ankle movements during swing) on two consecutive days. Capsaicin cream was applied around participants' ankle on both days for the Pain group, while the Control group was always pain-free. Changes in movement errors caused by the perturbation were measured to assess global motor performance; temporal distribution of errors and electromyographic activity were used to characterize motor strategies. Pain did not interfere with global performance during the acquisition or the retention phases but was associated with a shift in movement error center of gravity to later in the swing phase, suggesting a reduction in anticipatory strategy. Therefore, previously reported retention deficits could be explained by contextual changes between acquisition and retention tests. This difficulty in transferring skills from one context to another could be due to pain-related changes in motor strategy.

1. Introduction

Pain can influence the way we move in several manners, ranging from total avoidance of potentially harmful movements to more subtle changes in muscle recruitment [1]. While several studies have described the immediate effect of pain on motor performance [2], its effect on motor learning has been less investigated [3–10]. Among the studies who did look at the effect of pain on motor learning, only a few have considered its impact on the retention of new motor skills [8–10], rather than simply looking at improvement during practice (i.e., skill acquisition).

The impact of pain on locomotor learning is of particular clinical importance, given that neuropathic pain is highly prevalent in populations that have to perform locomotor learning as part of their rehabilitation, such as patients with incomplete spinal cord injury or lower limb amputees starting to use a prosthesis [11–13]. The only study so far that has looked at the effect of pain on a locomotor learning task showed that cutaneous pain induced by topical application of capsaicin (an experimental model of neuropathic pain) impairs the retention of motor learning despite normal performance during the acquisition phase [8]. In this study, pain was applied only during initial training (motor acquisition) and subjects were pain-free when retested for retention on the following day [8]. Based on these results, it has been suggested that cutaneous pain could interfere with neural processes associated with consolidation of motor learning.

An alternative hypothesis however is that as pain alters the context in which motor training occurs, being tested in the same task but in the absence of pain might in some sense be considered as a transfer test rather than a retention test. Therefore, poor retention might potentially be explained by changes in the pain context between motor acquisition

and retention testing rather than by an interference with the consolidation process per se. According to the specificity of practice hypothesis [14], it is expected that the performance of participants in a retention test will be optimized if the conditions of testing are identical to the conditions of skill acquisition. In the central nervous system (CNS), sensory information available during motor practice would be associated with the goal of the task and the state of the motor system to form a representation of the motor skill, which would contribute to the specificity of practice effect [14, 15]. Another aspect that might impact the ability to transfer a motor skill from a "pain context" to a "pain-free context" is the fact that pain has been reported to influence motor strategies used during motor adaptation tasks, even when the global performance itself is not affected [9].

The objective of the present study was to evaluate the effect of tonic experimental pain on performance and motor strategies used during the acquisition and retention phases of motor learning in a locomotor adaptation task. In contrast to our previous study [8], pain in the current was induced during both phases of motor learning. If pain directly interferes with processes involved in the consolidation of motor skills, impaired retention with pain should be observed as previously [8]. Alternatively, the absence of impaired retention would support processes involved in the specificity of practice hypothesis described above.

2. Method

Thirty-nine healthy participants were recruited among the university student population. Participants included in the study did not report any pain unrelated to the experimental pain stimulus and were able to achieve stable gait with the robotized orthosis. Eligible participants were randomly allocated to a Pain and a Control group, performing the motor task with or without experimental pain, respectively. However, the Control group was voluntarily oversampled, and it is used as the comparison group for several studies. Technical problems delayed the experiment for two participants of the Pain group, which resulted in their pain vanishing before the adaptation phase. They were therefore excluded from the analyses. The final sample was composed of 24 participants in the Control group (10 women, 25.8 ± 0.85 years old) and 13 in the Pain group (8 women, 26.1 ± 1.15 years old). Groups did not differ in terms of age (t-test: $p = 0.857$) or sex (Khi-2: $p = 0.248$). All participants provided their written informed consent and the ethics institutional review board approved the project (Institut de Réadaptation en Déficience Physique de Québec, Project #2010-212).

2.1. Experimental Procedure. Participants performed the same locomotor adaptation task on two consecutive days. Motor acquisition was evaluated on Day 1 and retention on Day 2. The locomotor adaptation task consisted in walking on a treadmill while overcoming a perturbation of the ankle movement applied by a robotized ankle-foot orthosis (rAFO) [16, 17]. In such task, the perturbation initially causes large deviations in ankle trajectory, termed movement errors. When continuously exposed to the perturbation, participants adapt to the perturbation by modifying their motor behaviour and gradually reduce their movement error through the training session. When the same task is performed after a delay without training, participants' performance is usually better than their performance on their first exposure to the perturbation, demonstrating retention of motor learning [8, 18].

During all experimental procedures (Figure 1), participants walked on a treadmill at a speed of 1 m/s while wearing the rAFO on their right lower limb. On Day 1, all participants began the experiment by walking normally (rAFO actively cancelling its own inertia in order to allow natural gait [16]) for 5 to 10 minutes without any painful stimulation (Baseline 1). This allowed the quantification of participants' normal gait pattern with the rAFO when they are free of pain. Afterward, the main experiment consisted of 15 to 20 minutes of treadmill walking without interruption. Pain was induced just before this walking period for the Pain group. During the first 5 to 10 minutes of the main experiment, participants walked normally as in Baseline 1 (Day 1: Baseline 2; Day 2: baseline). Then, the rAFO applied a force field resisting right ankle dorsiflexion during midswing (parabolic force field, peak amplitude of 4.8 ± 0.1 Nm at $81 \pm 1\%$ of gait cycle, 150 ms duration) at each stride for 5 minutes (adaptation) [8, 19]. Participants were not told about the exact time at which the force field would be turned on. They were instructed to "overcome the perturbation in order to walk as normally as possible." Finally, participants walked again without the force field during 5 minutes in order to recover their normal walking pattern before leaving the laboratory (washout).

2.2. Experimental Pain Induction. A ~1 cm wide band of capsaicin cream (1%) (~1 mm thick) was applied around the right ankle of Pain group's participants on both days, between Baseline 1 and Baseline 2 on Day 1 and before baseline on Day 2. Participants were asked to rate the intensity of their pain verbally on a Numerical Rating Scale from 0 (no pain) to 10 (worst pain imaginable) every 3 minutes throughout the experiment. The main experiment started once pain intensity reached a plateau (~30 minutes). On Day 1, a 30-minute wait period was imposed to the Control group between Baseline 1 and Baseline 2 for intergroup consistency.

2.3. Data Collection. Relative ankle angle in the sagittal plane was recorded with an optical encoder attached to the rAFO. A load cell placed in series with the rAFO's actuator recorded the forces applied to subjects' ankle. A custom-made pressure sensor placed under the right heel served as a footswitch. Bipolar surface electromyographic (EMG) activity was recorded from right tibialis anterior (TA; ankle dorsiflexor) and soleus (SOL; ankle plantarflexor) muscles. The electrodes were placed on shaved and cleaned skin in the location recommended by SENIAM for the SOL muscle [20]. For the TA, the electrodes were placed just under the calf band of the rAFO, as close as possible to the muscle belly. Electrode placement was marked on participants' skin on Day 1 to ensure between days consistency in EMG measurement. EMG signals were amplified 2000 times (custom amplifier;

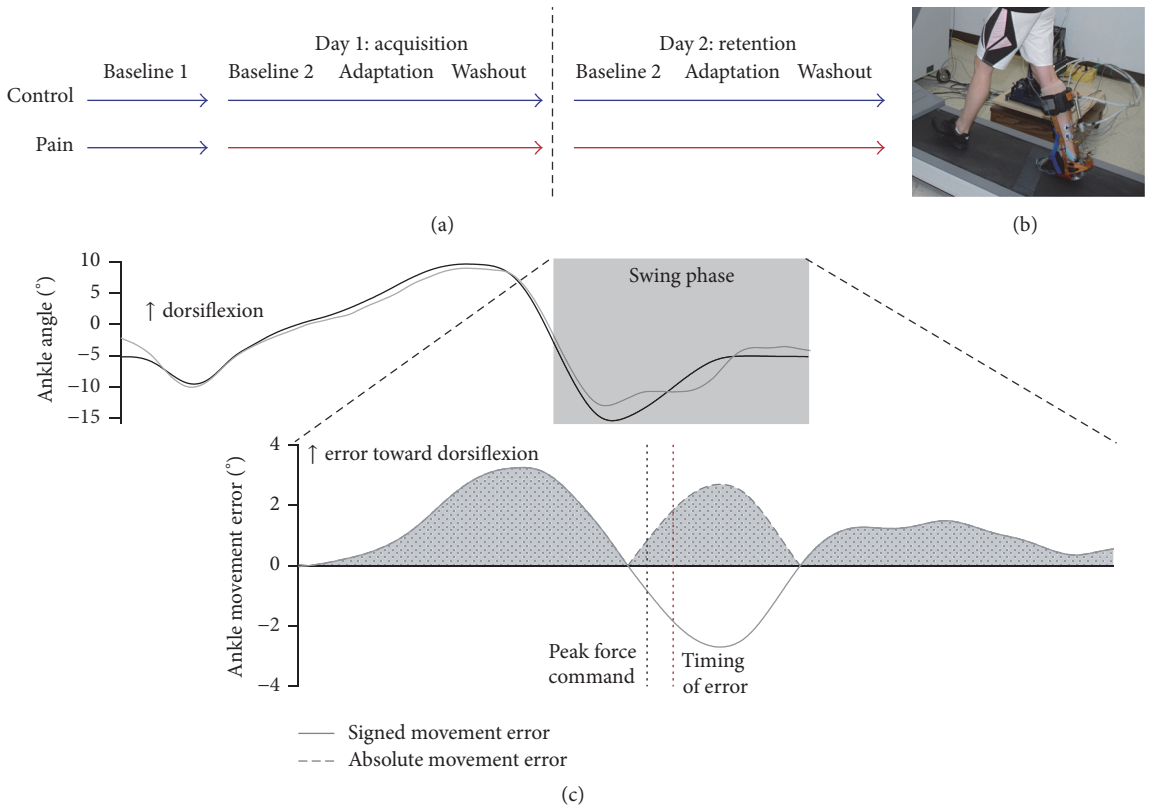

Figure 1: (a) General protocol of the experiment: blue and red arrows illustrate phases of the experiment performed without and with pain, respectively. (b) Robotized ankle-foot orthosis (rAFO). (c) Ankle kinematics outcome measures: the upper panel presents ankle angle during baseline gait (black) and adaptation (gray) for the whole stride duration. The lower panel illustrates the signed and absolute ankle movement error during the swing phase. The gray shaded area illustrates the mean absolute error outcome measure. The black and red dotted lines show the peak force command and the timing of movement error, respectively.

10–500 Hz Bessel filter) and all channels were sampled and stored on a desktop computer at 1 kHz/channel using custom data acquisition software.

2.4. Data Analysis. EMG data were digitally filtered using a 2nd-order zero-lag Butterworth filter (20–450 Hz bandwidth) and rectified. Thereafter, an envelope was extracted using a 9-point moving average filter [21]. Ankle angle data were filtered with a 2nd-order zero-lag 15 Hz low-pass Butterworth filter. Relative ankle angle was analysed in a period slightly longer than the swing phase: data were synchronised from the middle of the push-off to the right heel strike and time was normalised on 1000 points [8]. EMG analysis window was extended by 30% to include the beginning of TA stance-to-swing burst's onset.

2.4.1. Ankle Kinematics Outcome Measures. A baseline ankle angle template was constructed for each participant by averaging point-by-point ankle angle data for 45 of the last 50 strides of the baseline period (the five less representative strides were removed to limit outlier influence). On Day 1, Baseline 2 data were used to generate baseline ankle angle template. Then, ankle movement error curves were computed by subtracting the baseline template from each stride of the adaptation period. Note that ankle movement error curves of a given day were generated using baseline template of the same day.

Two different variables were derived from these error curves: (1) the mean absolute error, reflecting the general performance of the subject (i.e., the ability to walk "as normally as possible"); and (2) the relative timing of error (providing insights on motor strategies).

The mean absolute error was calculated for each stride of the adaptation period by averaging the rectified movement error curve during the whole swing phase [8].

The relative timing of error, a measure of the temporal center of error distribution relative to the peak force command, was calculated using the following equation for each stride of the adaptation:

$$\text{Relative timing of error} = \frac{\sum_{i=1}^{1000} |\text{Error}_i| \times i}{\sum_{i=1}^{1000} |\text{Error}_i|} - \text{Peak force command}, \quad (1)$$

where Error_i is the absolute amplitude at the ith data point of the movement error curve and Peak force command is the data point when the force command reached its peak

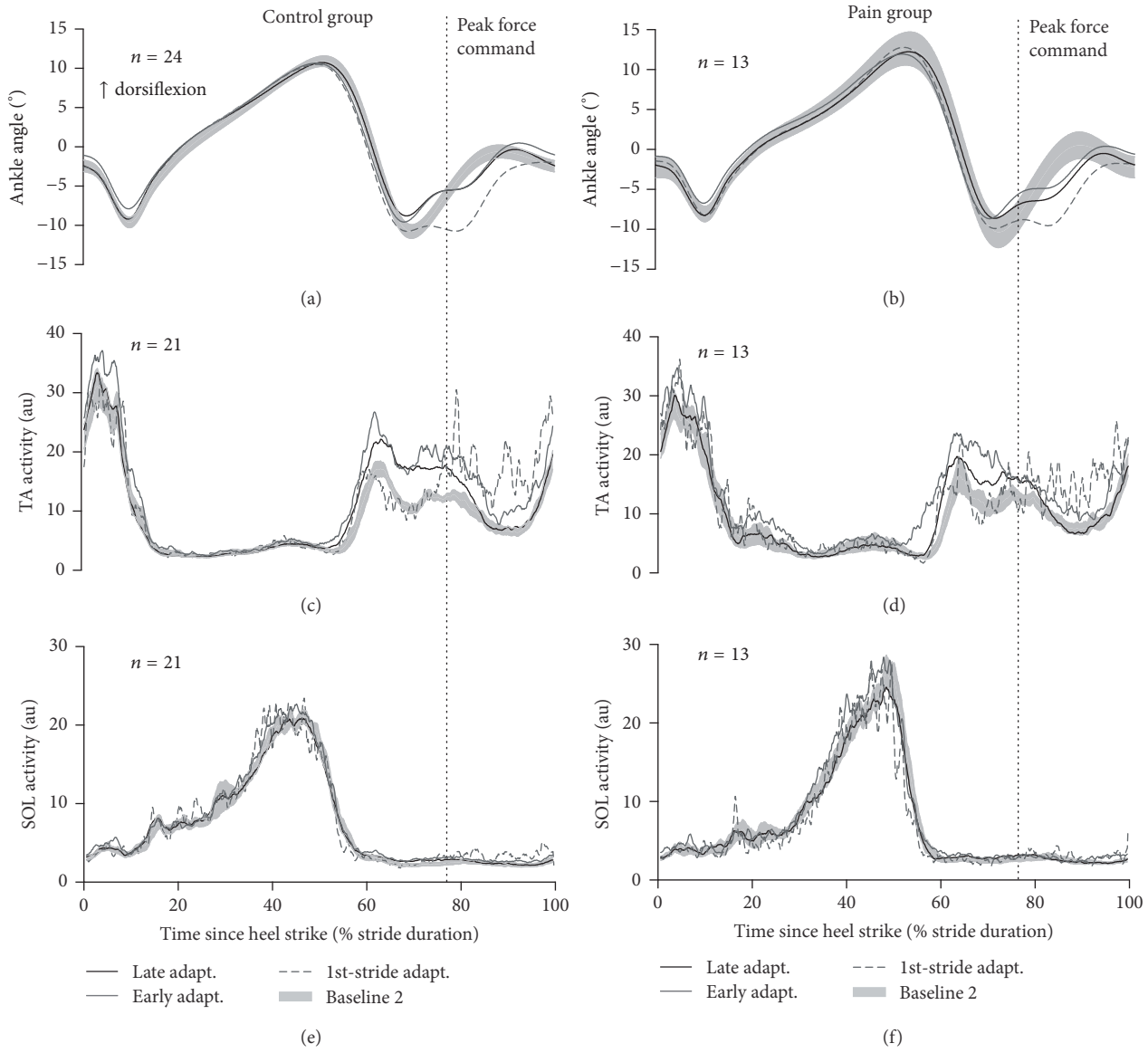

Figure 2: Summary of the results of the acquisition of motor skill (Day 1): (a), (c), and (e) show Control group averaged ankle angle (a), TA activity (c), and SOL activity (e) signals. (b), (d), and (f) present the same signals for the Pain group. The vertical dotted lines indicate the timing of the peak force command during the adaptation period. The shaded gray areas present each group baseline data (mean ± SEM). The gray lines illustrate the first stride (dashed line) and strides 2 to 11 (early adaptation; full line) of the adaptation period while the black line presents data during late adaptation (strides 151 to 200).

value. This variable provides information about the strategy used to overcome the perturbation during adaptation. Smaller relative timing of error suggests that participants used a more anticipatory strategy (i.e., movement is mainly modified *in preparation for* the perturbation) while larger relative timing of error suggests that participants are more reactive (i.e., movement is mainly modified *in response to* the perturbation).

2.4.2. Electromyography Outcome Measures. Visual inspection of EMG data (Figures 2(c)–2(f)) revealed that changes in EMG activity during the adaptation period were limited to the TA muscle as observed in Blanchette et al. 2011 [19]. Therefore, EMG analyses only focused on this muscle. Changes in TA activity during adaptation were quantified by computing the TA ratio during this period relative to baseline. A TA ratio vector was calculated using a point-by-point ratio of TA activity during the adaptation period over its activity during baseline. TA ratio was summarised in three outcome measures by averaging the TA ratio vector for the whole analysis window duration, as well as before and after the peak force command. The former variable informs about the global changes in EMG during the adaptation. The latter two variables are related to anticipatory and reactive strategies used by participants to overcome the force field, respectively. TA

ratios were linearized with a $\log_2$ transformation for statistical analyses while descriptive statistics on untransformed data are presented in the text.

2.5. Statistics. To quantify the effect of pain on the acquisition and retention of motor learning, 3-way repeated measure ANOVAs (time: early (strides 2 to 11) versus late adaptation (strides 151 to 200), day: Day 1 versus Day 2, group: Control versus Pain) were used for the mean absolute error and TA ratios. The first stride of the adaptation period was not a priori included in the statistical analysis, as participants did not know when the perturbation would be turned on. A generalised estimation equation for gamma distributions with log links was applied to the relative timing of error variable using the same design (time × day × group) [22]. The Benjamini-Hochberg correction for multiple comparisons was applied for post hoc analyses [23]. Data are presented in the text and figures as mean ± standard error of the mean (SEM). Level of significance was set at $p < 0.05$.

3. Results

3.1. Experimental Pain Intensity. The intensity of the pain induced by capsaicin was consistent between days (Day 1: 5.6 ± 0.7; Day 2: 5.5 ± 0.7; ICC: 0.842; paired t-test $p = 0.787$), confirming that the Pain group participants were in similar conditions for the evaluation of motor acquisition and retention.

3.2. Effect of Pain on Baseline Gait Parameters. Consistent with previous report [8], the mean absolute ankle angle difference and TA activity ratio between Baseline 1 (measured pain-free in both groups) and Baseline 2 (assessed with pain in the Pain group) were not different between groups (ankle kinematics: t-test $p = 0.147$, TA activity: t-test: $p = 0.916$). These results indicate that any difference in the acquisition of the motor adaptation is unlikely to be accounted for by a direct impact of pain on baseline gait.

3.3. Effect of Pain on Motor Learning. Figure 2 qualitatively illustrates the results on the effect of pain during the acquisition phase of motor learning (i.e., Day 1). Quantitative analyses are presented in the subsequent sections. The upper panels (Figures 2(a) and 2(b)), depicting ankle kinematics, shows that participants in both groups initially had large movement errors on their first stride of exposure to the perturbation but then quickly modified their motor behaviour. Actually, most kinematic changes occur in the first strides of exposure, as there is a larger difference between the first stride and early adaptation (average of strides 2–11) than that between early and late adaptation (average of strides 151–200). The middle panels (Figures 2(c) and 2(d)) show that this reduction of movement errors is achieved through an increase in TA activity. On the first stride of the adaptation period, increase in TA activity occurs only late in the swing phase (after the vertical line depicting the peak force command). This is explained by the fact that the perturbation is unexpected, and as a result the response to the perturbation is purely reactive.

Table 1: Post hoc analyses for the time × group interaction on the relative timing of error variable. Uncorrected p values are presented. According to the Benjamini-Hochberg procedure, the critical p value = $\alpha/m * i$, where m corresponds to the number of hypotheses tested ($m = 4$) and i corresponds to the rank of the tested hypothesis based on the uncorrected p value.

	Between groups Control versus Pain		Within group Early versus late
Early adaptation	$p = 0.321$	Control	$p = 0.007$[a]
Late adaptation	$p = 0.076$	Pain	$p = 0.048$[b]

[a]Critical p value = $0.05/4 * 1 = 0.0125$; [b]Critical p value = $0.05/4 * 2 = 0.025$.

On the following strides (i.e., during early adaptation), the EMG increase is observed earlier in the swing phase, reflecting a more anticipatory strategy. The large increase in TA activity initially observed slightly diminishes over time (i.e., from early (strides 2–11) to late (strides 151–200) adaptation), reflecting fine-tuning of the motor behaviour through practice. The lower panel of this figure (Figures 2(e) and 2(f)) shows that no significant changes in SOL muscle activity occurred during the adaptation period.

3.3.1. Ankle Kinematics. Results for the mean absolute error are presented in Figure 3(a) depicting the stride-by-stride time course during adaptation and Figure 3(b) showing average value for this variable during early and late adaptation on each day. A day effect was observed, showing an improvement in performance for both groups from Day 1 to Day 2 (effect of day: $p < 0.001$). However, there was no time, group, or interaction effect for the mean absolute error (all $p > 0.156$). It is important to note that the absence of effect of time is related to the fast improvement of participants' performance in opposition to an absence of improvement. Indeed, if the early adaptation epoch is replaced by the first adaptation stride in the ANOVA, the effect of time becomes significant showing the clear improvement in performance during the adaptation period ($p < 0.001$).

The time course of relative timing of error variable and the average for early and late adaptation epochs are presented in Figures 3(c) and 3(d), respectively. Results show a significant time × group interaction ($p = 0.005$; all other $p > 0.233$). Post hoc analyses were therefore performed by averaging Day 1 and Day 2 data and are presented in Table 1. For the Control group, the relative timing of error changes toward smaller values from early to late adaptation suggesting that participants without pain used a more anticipatory strategy to overcome the perturbation with practice. In contrast, for participants with pain, the relative timing of error tended to change toward larger values during the adaptation period suggesting less anticipatory strategy with practice. Moreover, the Pain group tended to use less anticipatory strategy during late adaptation then the Control group.

3.3.2. EMG. Significant effects of time were observed for all three TA outcome measures (ANOVA time: $p \leq 0.001$). No effects of group, day, or interactions were detected (all

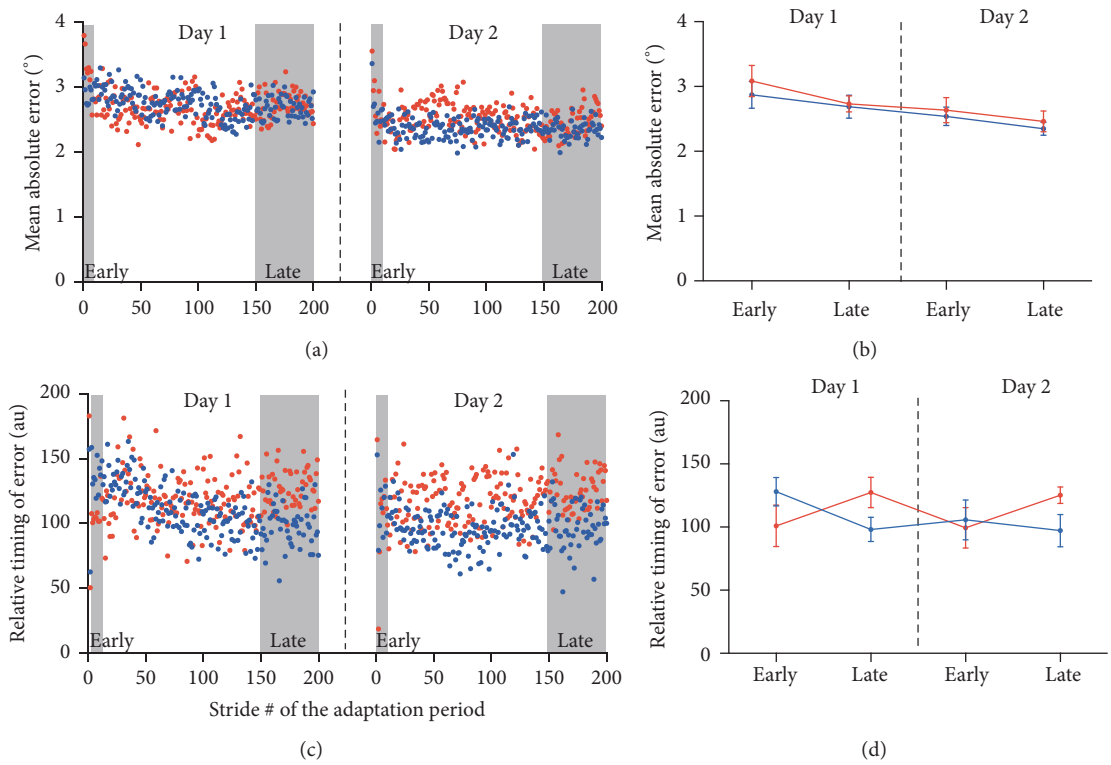

Figure 3: Results for ankle kinematic outcome measures: (a) and (c) present Control (blue) and Pain (red) group averaged time course of the mean absolute error (a) and relative timing of error outcome measures (c) for each day. Gray areas highlight the strides used for the computation of early and late adaptation presented in (b) and (d) (mean ± SEM).

$p > 0.134$). Therefore, the effect of time is presented with more detail for the whole sample averaged across days and only for the global TA ratio variable. After a rapid and important increase in TA activity during early adaptation (Early adaptation = 138±6% baseline TA EMG), participants slightly decreased their TA activity (Late adaptation = 113 ± 3% baseline TA EMG). Importantly, however, TA EMG activity remained higher during the adaptation period compared to baseline at all time points (one sample t-test: total TA ratio versus 0, all $p < 0.006$).

4. Discussion

Results of the present study show that cutaneous pain does not interfere with global performance during the acquisition and retention of a locomotor adaptation when skill acquisition and retention tests are both performed in the same context (i.e., with pain). Although global performance was unaffected by pain, the pattern of kinematic errors (relative timing of error) suggests that participants in the Pain group used a different motor strategy in order to overcome the force field compared to those of the Control group. Participants in the Control group shifted the relative timing of error with practice toward lower values suggesting a greater usage of anticipatory strategies (or a greater decrease in reactive errors) while the Pain group tended to show the opposite behaviour. However, no between groups differences were observed at any time point of the experiment on this variable despite the presence of a significant time × group interaction. Moreover, changes in TA activity across time were not different with or without pain. It is therefore difficult to interpret the effect of cutaneous pain on motor strategies used during locomotor adaptation thoroughly. The relatively small sample size of the study may have limited the power for some comparisons (especially for relative timing of error post hoc where trends were observed).

The fact that cutaneous pain did not influence the global performance of participants during the *acquisition* of the locomotor adaptation task is in line with our previous findings [8]. However, contrary to the results obtained with capsaicin applied only during the acquisition of motor skills [8], no interference with the retention of motor learning was observed when both the acquisition and retention were tested with pain. Those opposite results between these two studies using otherwise similar experimental paradigms suggest that the motor skills acquired while training in the locomotor adaptation task can be consolidated into the CNS even in the presence of pain. However, based on the results of Bouffard et al., 2014, the addition of cutaneous pain during motor acquisition appears to modify the representation of the motor skills into the CNS sufficiently to induce retention (or transfer) deficit when the same task is performed again without pain. The fact that participants of each group adopted different motor strategies during the locomotor adaptation emphasises the fact that motor skills can be acquired differently with pain although the task goal may still be reached. Previous studies

have shown reorganisation of muscle activity with pain or alterations in kinematics while maintaining the global motor performance intact in line with changes in motor strategy observed in the present study [9, 24, 25].

The performance decrement with the change in context between the acquisition and retention of a motor skill is in accordance with the specificity of practice hypothesis [14]. In the force field adaptation literature, a concept similar to the specificity of practice is often studied by evaluating the effect of matching various contextual cues to different pattern of force fields that are normally impossible to learn simultaneously because they require opposite motor strategies (e.g., clockwise versus counterclockwise perturbation during reaching movements). Reduced interference when each force field is associated with a different contextual cue is interpreted as a proof that the contextual cues allow the independent coding of motor skills involved for each adaptation [15, 26, 27]. Different contextual conditions can be manipulated to affect performance during retention tests and can be analyses in relation to the specificity of practice hypothesis. Those contextual conditions can be grouped into three categories: task-related sensory manipulations, task-related motor state manipulations, and task-unrelated (or indirectly related) manipulations. The impact of pain on factors involved in each of these categories will be addressed in order to give potential explanation of the present results.

Removing, adding, or disrupting the primary sources of feedback between the acquisition of a motor skill and retention test leads to results in line with the specificity of practice hypothesis [15, 28, 29]. It has been hypothesised that, during the acquisition of a motor skill, individuals learn to combine all feedback sources available to guide their performance. By removing (or adding) a dominating source of feedback during a transfer test, participants need to modify the way they integrate the information on which they rely during the motor task, leading to a performance decrement [14]. Disrupting a source of feedback without completely removing it also leads to similar results [15, 30]. In the present study, it is unlikely that participants learnt to rely on the sensory feedback caused by capsaicin application as the pain induced was tonic and unrelated to movements. However, pain can impair proprioceptive and cutaneous perception [31, 32], which are the primary sources of feedback during the locomotor adaptation task studied.

Other authors suggested that, during motor learning, the motor commands needed to reach the task goal are mapped as a function of the limb state [33]. Modifying the limb state during motor training, for instance, by modifying the location of reaching movement during motor adaptation, results in findings consistent with the specificity of practice hypothesis [15, 27]. In line with this view, it could also be expected that a manipulation of the input-output properties of the neural structures involved in the control of movement would influence the way motor skills are coded. Pain can exert such influence as some studies have shown changes in the excitability of different spinal and cortical neural network involved in motor control [34–36]. If an individual trains to a motor task with pain, he would learn to associate its motor commands to given outcomes. If pain disrupts the excitability of the neuronal structures involved in the motor task, this input-output mapping would be equally disrupted. Thus, when the individual would be tested for retention without pain to the same motor task, he would recover an erroneous control function, which would result in a performance decrement.

The effect of pain on variables directly involved in the motor task such as the feedback sources or the state of the motor system is not the only explanation for its context dependent effect on retention of locomotor adaptation. Manipulation of contextual characteristics not directly impacting the motor task can influence retention/transfer testing as well [15, 26, 37, 38]. For instance, it was shown that participants trained in various novel motor tasks (golf putting, wall climbing, or basketball free throw) in a low anxiety generating environment performed worse when tested in a high anxiety generating environment than participants who trained with anxiety. Conversely, participants who trained with anxiety had lower performance when subsequently tested without anxiety [37, 38]. This suggests that the variability between contexts where a skill is trained versus retested (or used in everyday life) might have a more deleterious effect on retention (or transfer) than a *negative* context in itself (e.g., pain, anxiety). This potentially has significant clinical implications given that, in several populations with pain, pain intensity (as well as mood) is often quite variable from one day to another [39–41].

5. Conclusion

While cutaneous pain during locomotor training was previously reported to interfere with retention when assessed in pain-free conditions, the results of the present study show that it does not prevent next-day retention when the pain context is similar between days. Together, these results suggest that the retention deficit previously reported could be explained by changes in contextual conditions between motor acquisition (with pain) and retention test (without pain), rather than to a direct impact of pain on the consolidation of motor skills. The fact that motor strategies used to improve performance appear to be modified by pain might contribute to the difficulty to transfer the new skills from one context to another. This has clinical implications given that pain intensity is known to be variable over time in several populations undergoing physical rehabilitation [40, 41].

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Exercise Training Promotes Functional Recovery after Spinal Cord Injury

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The exercise training is an effective therapy for spinal cord injury which has been applied to clinic. Traditionally, the exercise training has been considered to improve spinal cord function only through enhancement, compensation, and replacement of the remaining function of nerve and muscle. Recently, accumulating evidences indicated that exercise training can improve the function in different levels from end-effector organ such as skeletal muscle to cerebral cortex through reshaping skeletal muscle structure and muscle fiber type, regulating physiological and metabolic function of motor neurons in the spinal cord and remodeling function of the cerebral cortex. We compiled published data collected in different animal models and clinical studies into a succinct review of the current state of knowledge.

1. Introduction

Spinal cord injury (SCI) refers to a series of spinal injuries caused directly or indirectly by external factors. Depending on the segment affected by the injury, symptoms can range from motor and sensory dysfunction, muscle dystonia, and appearance of pathological reflexes. Primary SCI refers to the injury caused by the external forces acting directly or indirectly on the spinal cord. Secondary SCI refers to further damage caused by spinal cord compression, generated by edema, hematoma, compressive fractures, and broken intervertebral disc tissue. Spinal cord injury is characterized by high morbidity, high cost, and young patient age and it often leads to severe permanent disability. SCI not only affects the quality of patients' lives, but it also adds a burden to the family and the society. The latest statistics showed that the global incidence of spinal cord injury is about 236–1009/million people [1]. In USA, about 250,000 people suffer from varying degrees of SCI each year, with an annual rate of up to 28–50/million. Currently, there is a lack of effective clinical therapy to restore nerve function after SCI [2, 3]. Instead, exercise has become the most important quantifiable means for functional recovery [4, 5], and its mechanism has been studied by both clinical doctors and basic researchers. Here, we review recent researches on the mechanisms by which exercise training promotes functional recovery after SCI. Exercise not only directly strengthens paralyzed muscles and promotes motor function recovery but is also promoting brain remodeling, improves spinal microenvironment, and protects damaged distal motoneuron functions, at multiple levels and through various channels, thereby promoting functional recovery.

2. Effect of Exercise Training on Cerebral Cortex

In vitro studies have demonstrated that exercise can induce changes in the local neural circuitry, suggesting that afferent activity can activate cortical cells and promote nerve function remodeling [6]. Research on cortical reorganization after peripheral nerve injury also supports the idea of cerebral cortex plasticity [7]. Synaptic contact immaturity is implied

by the following observations: the length increase and density decrease of dendritic spines within 7 days in adult rats with the semisection but restoring to normal after 28 days [8]. This lays the foundation for exercise training promoting cortical reorganization after spinal cord injury.

It was shown that exercise after SCI could improve functional prognosis and induce cerebral cortex recombination in the somatic region. These observations have been recorded in both animal experiments and clinical studies. For example, rats exercises after SCI have shown a higher spontaneous firing rate of cortical neurons and enhanced forelimb sensory and sensorimotor stimulation (i.e., the forelimb motion projection area has been expanded to the lower limbs) [9]. In clinical studies, functional magnetic resonance imaging (fMRI) in patients with cervical spinal cord injury has shown that functional improvement after exercise is related to the degree of activation of the motor cortex [10]. Studies using transcranial magnetic stimulation and electroencephalogram (EEG) recordings have further confirmed changes in the cortical sensorimotor area [11]. Compared with healthy subjects, the sensorimotor cortex area associated with the muscle tissue above the damaged region is expanded in SCI patients. Positron Emission Computed Tomography (PET) studies have shown that, for SCI patients, wrist strength exercises increase the activation of the representative area of the contralateral upper limb motor cortex [12]. In addition, case studies have shown that, after complete C6 spinal cord injury, hand exercise can promote functional improvement and increase the representation of the hand muscles in the cerebral cortex [13]. Thus, after SCI, the functional remodeling of the cerebral cortex occurs to promote functional recovery [14].

Moreover, exercise can affect post-SCI remodeling of the brain function, through generation of systemic changes, such as improving blood circulation and neuroendocrine regulation and reducing spasticity [15]. Studies have confirmed that in animals with passive exercise training after spinal cord transection injury, the plasticity related neurotrophic factor, adenylate cyclase type 1 (ADCY1), and brain-derived neurotrophic factor (BNDF) increase in the somatosensory cortex, at levels significantly higher than in animals without training [16]. BNDF is important for neuronal growth and differentiation, and ADCY1 is important for establishment of long-term synaptic plasticity [17]. It was suggested that exercise training could promote brain function remodeling by inducing BDNF expression [18]. Graziano et al. found that, in animals with cycling training after thoracic spinal cord transection, tactile stimulation of the hind paw induced a neural response remapped to the cortical regions of front paws and forelegs under deep anesthesia [16]. Such training also improved the neurological cortical reorganization corresponding to the lower limbs, despite the interruption of afferent input from these limbs [16]. Active exercise can also increase the complexity dendrites in the dentate gyrus and the density of dendritic spines in rats [3], although the functional significance of these changes is not really clear. Similar studies have demonstrated that treadmill training can promote axonal growth [19, 20] and lesion proximal collateral sprouting and increase synaptic establishment [21]. Other similar findings in mature rat hippocampus have also shown that long-term treadmill training can increase the number of astrocytes and neural stem cells in the lower granular cell layer of the dentate gyrus. Exercise stimulates the proliferation of endogenous neural stem cells and generates neurotrophic factors, such as BNDF, which in turn regulate neural plasticity and improve motor function [22, 23]. Some studies have found that early exercise training after the corticospinal motor system injury can restore the contact of corticospinal tract (CST) and the movement projection of primary motor cortex (M1), thus increasing the number of cholinergic intermediate neurons in the ipsilateral and contralateral spinal cord and reducing the physical control disorder [24]. Therefore, passive exercise training of the areas below the spinal cord injury level can promote functional reorganization of the cortex.

Although brain function remodeling is an important mechanism for functional recovery after SCI, excessive function remodeling can result in pathological consequences such as illusion of limb sensation [25] and neuropathic pain [26]. Therefore, further studies and a deeper understanding of the mechanisms of cortical remodeling are necessary in order to adopt the best strategy after the interruption of sensory afferent pathways [27].

3. Effect of Exercise Training on the Structure and Function of Spinal Cord

After SCI, the distal neuron pathways undergo a wide range of chemical, electrophysiological, and structural changes, which result in spontaneous neurological remodeling [28]. The effects of exercise training on the structure and function of the spinal cord post-SCI include reconstruction of the neuronal structure; cellular proliferation and differentiation; activation of the metabolism and expression of neuronal substances and neurotrophic factors; and regulation of the cellular electrophysiological function.

4. Effect on Neuronal Structure

Experimental studies demonstrate that, after spinal cord injury, the length and density of the distal motor neuron dendrites and the overall neuron cell size are reduced, suggesting that SCI can cause secondary damage to injured distal motor neurons. Studies have even shown that, after thoracic SCI in rats, exercise training can increase the axonal length of the soleus and tibialis anterior motor neurons, within the lumbar spinal cord. Research using synaptophysin immunohistochemistry has shown that treadmill training can significantly increase the formation of the lumbar spinal synapses [3]. Similarly, stepping training after transection of new born rat spinal cord can cause significant pathway changes and increase motor neuron synapse activation by stimulating primary afferent fibers or white matter tracts [29]. The expression of synaptophysin and PSD-95 in the area surrounding the ventral horn of the spinal motor neurons is significantly higher in rats training on the treadmill than in the untrained group [30]. Exercise training can activate the motor neuron N-methyl-D-aspartate (NMDA) receptor

[31], by increasing the expression of BNDF and TrkB (tyrosine kinase gene) in spinal cord [32]. NMDA receptors further regulate neuronal survival, dendritic structure, synaptic plasticity, and neuronal circuits. Active training can also increase the expression of neurotrophic factors and nestin-GFP around the ependymal area. This promotes ependymal cell proliferation and differentiation into neural precursor cells (NPC) and further into oligodendrocytes and astrocytes [33], resulting in nerve regeneration and improved functional recovery.

Oligodendrocytes play a key role in leading and efficient signal transmission, and in maintaining and protecting a normal neuronal function. The immature oligodendrocytes markers, transferrin and cyclic nucleotide phosphohydrolase (CNP), increased significantly after seven days of active training [34]. The current consensus is that exercise can induce the neurotrophic factor BNDF, insulin-like growth factor I (IGF-I), and vascular endothelial growth factor (VEGF), to promote spinal oligodendrocyte regeneration [35]. Active training can also elevate the levels of glial fibrillary acidic protein (GFAP), regulate the astrocytes aggregation, and promote astrocytes maturation and differentiation [36].

5. Effect on Cell Biochemistry/Metabolism

In rats with treadmill training, the nucleolar area of motoneurons increases and becomes surrounded by basophilic granules. Also, the staining intensity of glucose-6-phosphate dehydrogenase increases, indicating a boost in protein synthesis [37]. After training, motoneurons can transport more axonal protein, through either forward or reverse transport, and thus improve the overall adaptability of the motor units. For example, synaptic protein SNAP25 links synaptic vesicles and presynaptic membrane and motor neuron axons transport synaptic proteins SNAP25 with high selectivity after training [38]. Other proteins, such as the enzyme malate dehydrogenase and the trophic factor calcitonin gene-related peptide, are present in higher amounts in the motoneurons. Post-SCI cycling training can also raise the amount of phosphocreatine-S6 (P-S6) expressed by intermediate neurons and cause dendrites branching of motor neurons [39].

6. Effect on Electrophysiological Properties of Motor Neurons

Exercise training can alter the electrophysiological properties of transacted spinal motoneurons, such as the hyperpolarization of resting membrane potential and voltage threshold, the speed increase of action potential, and the increase of after-hyperpolarization potential amplitude of action potential. Studies have shown that depolarization of resting membrane potential (RMP) and spike trigger level (STL) occurs four weeks after complete transection of the thoracic spinal cord [40]. After training, the RMP can become hyperpolarized [41], thus altering the inhibition of the rubrospinal tract on stepping and promoting functional recovery [29]. Stepping training can enhance muscle spindle afferent signals [42, 43], promote aspartate NMDA receptors functioning [44], and increase the amplitude of the incoming signal of the motoneuron synapsis, causing an after-hyperpolarization in the action potential of motoneurons. In addition, the ventrolateral spinal cord white matter (VLF) can also induce changes in the electrophysiological activity of motoneurons.

In rats with SCI, a change in the after-hyperpolarization potential (AHPd) affects the rhythm, intensity, and duration of interneuron activity which affects the stepping function [45]. Passive exercise can enhance the magnitude of excitatory postsynaptic potentials (EPSP), increase the number of motoneurons that accept incoming signal, steer AHPd towards normal level, and restore normal stepping [46]. Ultra-microstructural analysis has shown that, after spinal cord transection, exercise training can increase the magnitude of gastrocnemius motor neuron (MNs) excitatory postsynaptic potential (EPSP) but has no significant effect on the inhibitory postsynaptic potential (IPSP).

Spinal cord transection injury results in impaired stepping ability, causes reduced incoming signal from distal motoneuron synapses, enhances inhibitory effects, and thereby inhibits α- and γ-MNs activity. Studies suggest that this may be related to the significantly more numerous inhibitory F-type enlarged terminals than in the excitatory S-type enlarged terminals. It could also be due to the structural changes occurring in the parallel C-type and M-type enlarged terminals of γ-MNs cell bodies. Exercise training can maintain a normal ratio between the excitatory S-type and the inhibitory F-type enlarged terminals of γ-MNs and α-MNs [47], as such maintaining the ratio between excitatory and inhibitory signals to improve stepping function.

7. Effect of Exercise Training on the Structure and Function of Skeletal Muscles

After SCI, paralyzed muscles exhibit decreased fiber diameter, reduced voluntary contraction force, decreased metabolism, delayed conversion of slow-twitch to fast-twitch fibers, and a cross-sectional area comprised mainly of type I fibers. Currently, it is believed that skeletal muscle atrophy is characterized by lost [48, 49] or apoptotic muscle fiber nuclei [50], suggesting that reduced myoglobin nuclei number leads to "nuclear apoptosis."

The lost function characterizing muscle atrophy can be restored by several methods, primarily by inducing IGF-1 [51], Pax7, and other molecules that promote myogenic cells (satellite cells) activation, proliferation, and differentiation and participating in muscle fibers (muscle cells) repair [52]. Studies have shown an increase in the soleus IGF-1 protein levels after spinal cord injury. After treadmill training, soleus IGF-1 shows additional increase, to activate proliferation and differentiation of satellite cells [53], and increase in the muscle fiber numbers. This implies that exercise training after SCI can enhance satellite cell activity and promote muscle fiber formation. Endurance training seems to increase terminal branching of nerves at the neuromuscular junction [54], although results are ambiguous [55].

Studies have shown that in cats with SCI the expression the levels of myosin heavy chain (MHC) in the soleus can be restored after stepping training. After one week of weight-bearing stepping training after SCI, the wet weight of the plantaris, medial/lateral gastrocnemius, soleus, and

tibialis anterior muscles is significantly reduced. After three weeks of training, twitching and tonic tension peaks in the soleus muscle decrease significantly and the MHC expression in the extensor digitorum longus IIx increases. By 10 weeks, the muscle wet weight, contractile properties, and MHC levels returne to baseline levels, except for LG/MG atrophy [56].

8. The Effect of Combinatorial Strategy with Exercise

Although exercise training can improve neurological and skeletal muscle function by modulating the multilevel structures and function of the cerebral cortex, spinal cord, and skeletal muscle following spinal cord injury (SCI), current evidence suggests that exercise training has limited efficacy in improving motor function after SCI in rodents or cats [57–60]. Such inadequate effects are believed to be attributed to insufficient neurotrophic factor production induced by training. Therefore, in addition to exercise, more and more combinatory strategies have been investigated. Many studies have shown that combined therapy can significantly promote the recovery after SCI and relieve spasticity in rats compared to single treatments alone [61]. Current strategies focus on combinatorial effects of hematopoietic stem cells, neurotrophic factors, drugs, and electrical or magnetic stimulation. Tashiro et al. showed that neural stem cell transplantation combined with treadmill training significantly improved spinal cord pathway conduction and increased central pattern generator activity, resulting in significantly improved motor function [62]. Dental pulp stem cell transplantation not only promoted motor function recovery but also significantly reduced lesion cavity and glial scar formation [60]. Trophic support appears to be the key to effective combination therapy. The secretion of neurotrophic factors can be stimulated in the injured spinal cord by neural stem cell transplantation or exercise training [20, 63, 64]. Combining these two therapies can significantly increase neurotrophic factor secretion. Direct neurotrophic factor application combined with exercise training can also promote functional recovery following SCI [65]. Han et al. combined Glial cell line-derived neurotrophic factor (GDNF) with early rehabilitation significantly reduced pathological changes and motor dysfunction in patients with SCI [61]. Other neurotrophic factors such as Brain-derived neurotrophic factor (BDNF) and Neurotrophin-3 (NT-3) can also significantly increase BBB scores, indicating improved functional recovery [66]. The above studies suggest that trophic support from combinatorial treatment is an effective intervention to improve motor recovery after spinal cord injury.

In addition, many studies have shown that electrical stimulation or magnetic stimulation combined with exercise training can influence motor function in SCI patients [67]. Petrosyan et al. showed that spinal cord electrical stimulation combined with exercise training can induce sustained enhancement of synaptic transmission, thereby improving lumbar anatomical plasticity to promote motor function recovery [59]. Chao et al. demonstrated that functional electrical stimulation combined with treadmill training could activate intraspinal circuits to improve gait control [68]. After SCI, load-bearing training combined with functional electrical stimulation can activate ankle flexion to prevent swing phase drag, also reduced swing phase time and improved limb coordination [69, 70]. Sensory stimulation of the tongue combined with specific training significantly improved the balance and gait of patients with incomplete SCI [71]. There are also reports that repetitive transcranial magnetic stimulation combined with plate training can significantly reduce lower limb stiffness in patients with SCI [72]. Therefore, the combination of electrical or magnetic stimulation and exercise training could significantly improve motor function and maximize functional recovery, which provides a new perspective for clinical rehabilitation.

The effects of drug therapy combined with exercise training have also been reported. Intraperitoneal injection of fluoxetine combined with exercise training significantly increased BDNF in the hippocampus which promoted nerve regeneration and BBB score [73, 74]. The combined use of meta-chlorophenylpiperazine (mCPP) and quipazine in SCI not only improved BBB scores but also improved weight-bearing walking [66]. The implantation of polypyrrole/iodine (PPy/I) can protect nerve tissue and promote functional recovery [75]. If combined with treadmill exercise training, this effect is more significant [2]. Alluin et al. showed that combination therapy of chondroitinase ABC, neurotrophic factors, and exercise training not only enhanced active motor function recovery by enhancing neuroanatomical plasticity of the descending tracts (corticospinal tract and 5-HT pathway) but also significantly reduced the astrocyte proliferation and inflammation around lesions [76]. Transplantation of Schwann cells and olfactory ensheathing cells in the spinal cord of cats combined with chondroitinase ABC treatment significantly improved motor function [77]. Drug therapy combined with exercise training is more favorable in the treatment of SCI, suggesting that adjuvant drug treatment may have a better prognosis in SCI patients in the clinic.

In conclusion, exercise training can induce structural and functional changes in the cerebral cortex, spinal cord, and skeletal muscles, thus improving neural and muscular function following spinal cord injury. Exercise appears to promote nerve regeneration with functional restoration, to induce corticospinal pathway connectivity [36], to maintain the functional status of spinal cord neurons, to activate skeletal muscle satellite cells, and to promote muscle fiber regeneration. Exercise training combined with other treatments in SCI is the future direction with the most promise. More research is needed to optimize the specific training parameters, such as intensity, duration, frequency, and so forth. Also, the effect of exercise on SCI secondary complications (e.g., chronic pain, bladder and gastrointestinal dysfunction, muscle mass loss, osteoporosis, pressure ulcers, joint and muscle pain, fatigue, sleep problems, depression, and temperature control loss) is rarely discussed in literature and needs further exploration.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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