Corpus Callosum Functional Activities in Children with Cerebral Palsy

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ABSTRACT

Background: Since cerebral palsy (CP) is a corollary to brain damage, persistent treatment should accompany an alteration in brain functional activity in line with clinical improvements. In this regard, the corpus callosum (CC), as a connecting bridge between the two hemispheres, plays an essential role.

Objective: This study aimed to investigate the therapeutic effects of occupational therapy (OT) on CC functional activity and walking capacity in children with cerebral palsy.

Material and Methods: In this clinical trial study, 4 children with CP (8.25 ± 1.71 years) received 45 min OT sessions 3 times weekly for 8 weeks. Functional magnetic resonance imaging (fMRI) was acquired while conducting passive motor tasks to quantify CC activation. The pre-post activation changes in CC following therapy were quantified in terms of activated voxels. Walking capacity was evaluated using the timed-up-and-go (TUG), 6-minute walk test (6 MWT), and 10-meter walk test (10 MWT) in pre-and post-treatment.

Results: The number of activated voxels in CC indicated significant improvement in participants. Post-treatment activated voxels substantially exceeded pre-treatment active voxels. Clinical measures, including TUG, 6 MWT, and 10 MWT are improved by 11.9%, 12.6%, and 25.4%, respectively.

Conclusion: Passive task-based fMRI can detect the effects of OT on CC functional activity in children with CP. According to the results, OT improves CC functional activity in addition to gait and balance performance.

Introduction

Cerebral palsy (CP) with the rate of 2-3 per 1000 live birth is considered one of the most common causes of motor disability in childhood, which may accompany limited functional activity and reduce the quality of life [1-3]. An effective long-lasting intervention is needed to improve their balance and gait. The most popular treatments for children with CP are physical and occupational therapy (OT) in the first few years of life or soon after diagnosis [4-6].

In children with CP, the less affected brain hemisphere tries to compensate for the weakness of the more affected one due to the

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relationship between the two hemispheres. Therefore, the evaluation of the treatment effects on the corpus callosum (CC), which connects the left and the right hemispheres, is imperative. CC makes up the largest collection of white matter (WM) tissue found in the brain and is critical for tasks that require inter-hemisphere communication. It is essential to gain a thorough understanding of the functional activity between the two hemispheres and movement performances in children with CP to better investigate treatment effectiveness [7]. Severe white matter (WM) loss of the CC measured by magnetic resonance imaging (MRI) is associated with a poor gross motor function classification system (GMFCS) [8], showing that MRI may not be sensitive enough to detect microstructural impairments in WM. More advanced neuroimaging methods, such as functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) provide a more sensitive measure of WM microstructure and function in CC, respectively [9]. A larger corpus callosum size correlated with better motor performance in children born prematurely or with periventricular leukomalacia [10-12]. The communicative role of CC between the two hemispheres is particularly important for motor control [13].

In addition, fMRI is a neuroimaging tool employing MRI to image small changes in blood flow occurring with brain activity. In general, fMRI helps identify active areas of the brain, which are interactive in performing a particular function [14-17].

Task-based fMRI (T-fMRI) is a non-invasive method based on blood oxygen level-dependent (BOLD) techniques, which is widely adopted to identify brain regions that are functionally involved in specific task performance during scanning. T-fMRI provides many signals, reflecting functional brain activity, which results from each voxel of the brain during scanning [8,18-21]. Some researchers reported fMRI activation in WM, particularly the CC [22].

Since technical challenges make fMRI of the lower extremity difficult [23], few studies are conducted on the use of T-fMRI to investigate neuroplasticity in the rehabilitation of lower extremity in children with CP [24,25]. T-fMRI is also used to investigate brain plasticity due to body-weight-supported treadmill training (BWSTT) [24] and to capture neuroplastic changes after intensive rehabilitation in children with CP [26]. Furthermore, fMRI requires individuals to remain fixed in a restricted space for a long time, limiting the success rate of fMRI studies in healthy pediatrics. The situation is even more complicated in fMRI data acquisition for children with CP [27,28].

This study aimed to characterize the therapeutic effects of OT training on CC functional activity and walking capacity in children with CP. It is hypothesized that passive T-fMRI under sedation is an effective tool for detecting alterations in CC activity induced by physical activities in children with cerebral palsy.

Material and Methods

Subjects

In this clinical trial study, 4 subjects with spastic hemiplegia CP (two female and two male; 6–10 years old) were included, and inclusion criteria were defined as follows: modified Ashworth scale greater than 1 (MAS>1), hemiparetic, no history of surgery during six months before training, ability to stand independently for at least 30 s and walk independently despite reduced balance and speed. Subjects were excluded if they had received botulinum toxin injections within the past 2 months. Table 1 summarizes participants' characteristics and Figure 1 depicts axial T1 images of children with CP.

Training Protocol

OT is an essential part of a CP patient's overall treatment plan to promote children's ability to perform daily activities in a way that improves their quality of life with independent

Table 1: Participants' characteristics

Patient Number	Sex	More Affected Side	Age	Weight	Height
1	M	R	9	30	134
2	F	L	6	17	108
3	F	L	10	33	140
4	M	L	8	29	127

living. In this study, OT was conducted by an occupational therapist with a focus on gait and balance training at the rehabilitation center, and OT training was conducted 3 sessions (45 min) per week for 8 weeks and mostly concentrated on locomotion.

fMRI Instrumentation and Procedure

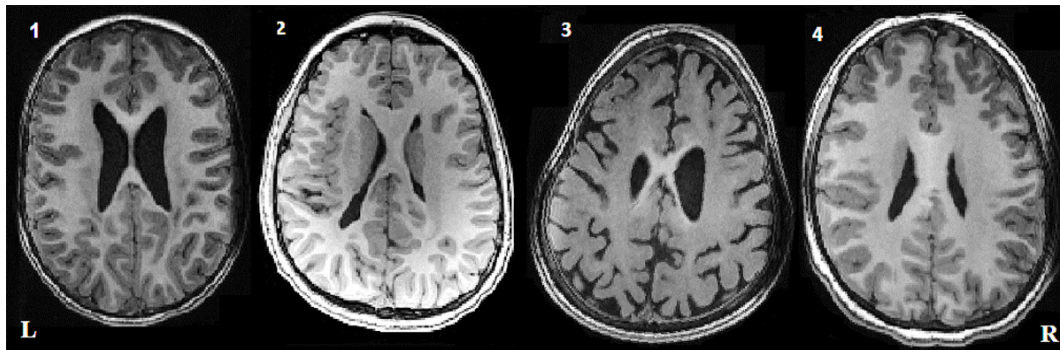In addition, fMRI acquisition included a passive task applied by a trained biomedical

Figure 1: Axial T1 images of children with cerebral palsy (CP)

engineer who completely flexed the patient's knees and extended back (Figure 2) over the range of motion (ROM) 1 time per second (1 Hz). For fMRI acquisition, a block design was used with 24-second motor activity alternating with 24-second rest for a total of five cycles.

Participants underwent MRI scans before treatment (pre-treatment) and after the 8-week treatment program (post-treatment); all children were sedated before undergoing MRI. The general anesthesia with intravenous Propofol administered at the lowest dose to keep patients asleep was supervised by pediatric anesthesiologists. All anesthetic information, including the sedation procedure and medications used for induction and maintenance, was documented in the medical record.

Further, fMRI data were acquired from all 4 children, and the fMRI scans were performed on a 3T scanner (GE, IKH hospital complex, Imaging Center) in 64 directions. The number of slices is 80 with a 3 mm slice thickness
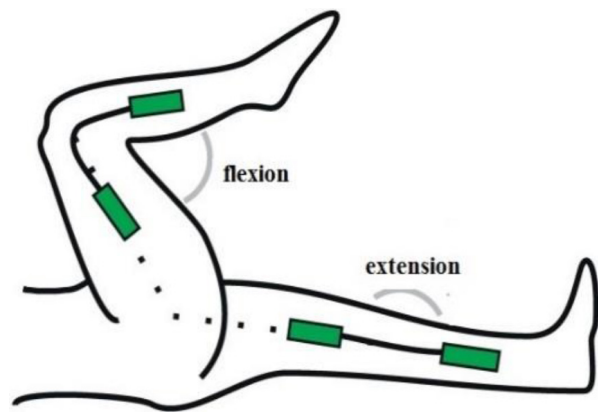

Figure 2: Knee passive tasks

(matrix=64×64, FOV=220 mm, TR=3000 ms, and TE=30 ms). High-resolution structural T1 images were attained (matrix=256×256, FOV=220 mm, TR=22 ms, TE=10 ms) with a 1mm slice thickness. Functional and anatomical images were obtained parallel to the anterior/posterior commissure line in an

axial direction. The subjects were placed in a supine position with padding around their head to minimize movement.

fMRI Data Processing

In this study, the fMRI of the brain (FMRIB) software library (FSL v6.02) was deployed to preprocess the fMRI data and perform statistical analysis. Standard preprocessing steps, including realignment, brain extraction, motion correction, spatial smoothing, denoising, and filtering were applied to fMRI data. The standard space (MNI152 atlas) was registered to functional data [29].

The region of interest (ROI) analysis, including the corpus callosum (CC), was selected from the Harvard-Oxford probabilistic atlas and then transformed into the individual's native space.

The fMRI images were realigned and co-registered to the mean functional image from the first session. The FSL procedure was followed to produce a non-brain mask for brain extraction. The movement parameters of the patients were included in the individual analysis to reduce motion artifacts. A Gaussian kernel with a $5\times5\times5$ mm^3 full width at half maximum (FWHM) and a high pass (HP) filter of 72 s was used to smooth fMRI images. The main goal of spatial smoothing is to suppress spatial noise and improve the signal-to-noise ratio (SNR). Multivariate exploratory linear optimized decomposition into independent components (MELODIC) was performed for denoising. Independent component analysis (ICA) was rerun in each subject's temporally concatenated data for all sessions [30-32].

First-level individual statistical analysis was performed to determine the significant brain areas, using the general linear model (GLM). Second-level models were used to estimate brain functional activity for the separate contrasts (passive movements > rest). Subsequently, a t-test was used to detect the significant difference for passive movements > rest contrast; all contrasts were reported for clusters comprising at least 10 voxels and the false discovery rate (FDR) with a *P*-value <0.05.

Clinical Evaluation of Gait and Balance

The common clinical parameters used in this study to evaluate walking capacity included:

• Timed-Up-and-Go (TUG): This simple test was used to measure the duration of the required task, including standing, walking, and sitting back to assess balance and mobility [33]. TUG was defined as the time for a subject to rising from a chair, walk 3 meters away, turn 180°, walk back to the chair, and sit back down while turning 180° [34].

• Six-minute walk test (6 MWT): This test was employed to measure the distance an individual can walk for a total of 6 min on a hard and flat surface representing walking endurance and was widely used in clinical practice, providing information about functional capacity [35].

• Ten-meter walk test (10 MWT): This test was used to measure the duration of a 10-meter walk to measure walking speed in meters/second and to determine gait, mobility, and vestibular function [36].

Results

Corpus Callosum Functional Activity

ROI analysis was used to measure the changes in brain activity of the CC detected by fMRI following the completion of training in each subject to consider the heterogeneity of the size and location of brain lesions in CP participants. The results revealed that the knee passive motor task successfully activated the CC in all subjects. For the knee task, CC showed significant enhancement in terms of the number of active voxels in most participants. ROI analysis in participants 1, 2, and 3 showed an enhancement in the number of activated voxels in the CC area. Participant 4 had fewer activated voxels following

treatment; the number of active voxels in CC is illustrated in Figure 3.

Table 2 explains the pre-and post-treatment results of ROI-based activation in the CC (*P*-value <0.05). The local maxima in Montreal neurological institute (MNI) coordinates and the most activated clusters were also described for each subject.

The average group results were used to determine the effectiveness of interventions.

Figure 4 shows the results of significant group activation changes for the CC region following the completion of the 24 OT sessions. These results revealed significant (*P*-value <0.05) difference in CC activation pre-and post-treatment.

Therapeutic Effects on Gait and Balance Impairment

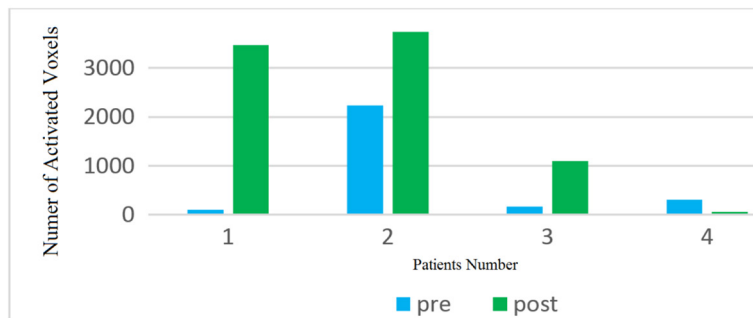Figure 5 and Table 3 describe the results of

Figure 3: Number of active voxels in corpus callosum pre-and post-treatment, at z>3.1

Table 2: Significant difference in activation between pre-and post-treatment in the corpus callosum (*P*-value <0.05)

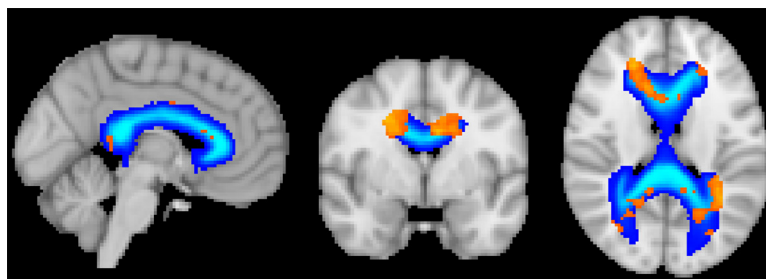| Patient Number	z	-10 log (*P* value)	Max (x, y, z)	# of clusters	Main Cluster Size
1	4.75	16	(36,-58,18)	5	296
2	10.2	58.7	(-44,-44,10)	9	2419
3	5.04	12.6	(-32,-60,20)	3	218
4	5.5	12.8	(24,-6,36)	5	233

Figure 4: Significant difference activation between pre-and post-treatment in children with cerebral palsy, as revealed by the passive movements > rest contrasts. The red to yellow voxel clusters represent significantly higher corpus callosum activation at *P*<0.05 (false discovery rate correction was utilized)
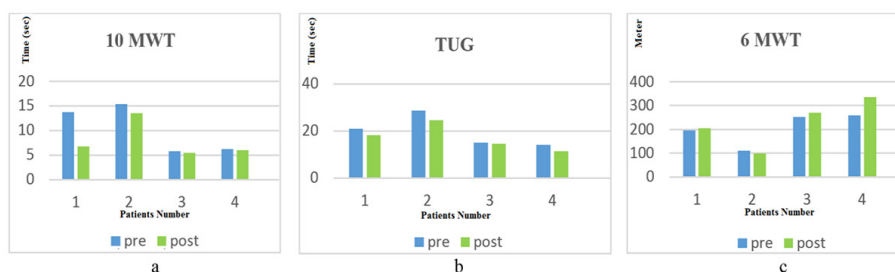
Figure 5: Pre-and post-treatment of clinical characteristics of walking capacity: **a)** 10-meter walk test, **b)** timed-up-and-go, **c)** 6-minute walk test

Table 3: Percentage of clinical characteristics improvements

Patient Number	10 MWT (%)	TUG (%)	6 MWT (%)
1	50.5	12.4	4.6
2	12.3	14	-10
3	5.4	2.1	7.1
4	33.5	19.1	28.8

TUG: Timed-Up-and-Go

clinical measures of walking capacity, including TUG, 6 MWT, and 10 MWT as well as their percentage changes following the 8-week training sessions for each subject. Balance and mobility measured by the TUG test improved by 11.9%; walking endurance evaluated by the 6 MWT increased by 7.6%; and walking speed measured by the 10 MWT enhanced by 25.4%.

Discussion

In this study, the therapeutic effects of intensive OT are characterized by walking capacity and CC reorganization in children with hemiplegic CP using passive T-fMRI. Further, the current study aimed to determine the impact of OT training on brain functional activity in children with CP. The passive motor task includes knee flexion to the extension over the ROM, conducted on all patients before and after the 24 training sessions, resulting in investigating therapy-induced CC activation alterations. Based on the findings, both CC activity and walking capacity are improved following the completion of OT training.

Furthermore, fMRI is highly sensitive to motion artifacts [7]. However, the patient was sedated with a sedative agent, which minimally hampered the neurophysiologic effects of administered motor and sensory stimulation to overcome this issue, this study obtained passive motion T-fMRI [37,38]. The effects of extremity movement under sedative conditions were already reported in the literature [35,36]. Passive motor tasks could activate most of the brain regions [39-41], such as the premotor cortex, parietal cortex, and contralateral sensorimotor cortex [40]. Additionally, brain activation associated with passive movements in children with unilateral CP (UCP) was evaluated [41]. However, passive T-fMRI was investigated in children with CP [41]; to the best of our knowledge, no evidence of passive T-fMRI is under sedation in this patient population. Furthermore, most studies on passive movement T-fMRI in healthy children and adults, adult stroke patients, and CP children were conducted without the use of sedation and examined brain activity in the motor cortex rather than the CC [28,41-43].

In this study, ROI analysis was used to identify the therapeutic effects of OT training on CC activation using fMRI in each subject. The activation patterns of the knee task for all the participants were compared using the same data acquisition parameters and analy-

sis techniques at the FDR corrected level (*P*-value <0.05). Subsequent data analysis and comparisons demonstrate that CC activation increased in 3 subjects and decreased in 1 subject after 8 weeks of OT training. Passive motor tasks used in this study produced consistent activation in the CC, which connects the right and left cerebral hemispheres. According to Figure 3, training-induced activation of the CC increased in subjects 1, 2, and 3, but decreased in the subject 4.

Studies that utilized OT, BWST, and Lokomat [44] for walking capacity improvement, mostly reported clinical enhancement rather than the characterization of brain reorganization [43-45]. However, few studies have examined neuroplasticity in gait rehabilitation using BWST in children with CP and adults with stroke [19,33,46]. The hemodynamic response (HR) of the sensorimotor cortices following treatment was reported to decrease in some of these studies, while others showed that cortical activation increased [41,43]. Furthermore, according to a limited number of fMRI investigations in children with UCP, increased contralateral activity may accompany functional gains. For instance, cluster-based M1–S1 voxel counts increased in three adults with UCP after virtual reality therapy [47]. In the current study, the results show both a decrease and an increase in CC activation after therapy.

The group means demonstrated an improvement in TUG, walking endurance, and walking speed. The improved clinical characteristics along with CC increased activation implies that intensive OT training may have the potential to promote effective brain reorganization, which can enhance walking ability in children with CP.

However, our findings were promising with respect to the investigation of therapy-driven enhancement of CC functional activities, the present study had a few limitations as follows: 1) few subjects could complete the required training sessions and attend the MRI sessions due to the intensive treatment schedule and sedative fMRI acquisition and 2) we were successful in detecting the changes in brain functional activity following OT, despite the suppressing effects of sedation, showing that the changes in brain functional activity following OT must be greater than those reported in this study.

Conclusion

The quantitative analysis of voxels activity can detect the signature of passive task movements in the fMRI and accurately measure the effects of treatment on brain functional activity in children with CP. Based on the results, the 8-week OT training has profound therapeutic effects on brain activity and walking capacity. Therefore, long and intensive OT training is expected to provide persistent therapeutic effects and cause neuroplasticity.

Acknowledgment

Authors' Contribution

MM. Mirbagheri and MR. Deevband conceived the idea. Introduction and manuscript of the paper was written by M. Ashtiyani, PM. Birgani and M. Soleimani. MRI data were collected by M. Ashtiyani and PM. Birgani. The method implementation and experimental studies were carried out by MM. Mirbagheri, M. Ashtiyani and SB. Jameie. Results and Analysis was carried out by M. Ashtiyani, PM. Birgani, MM. Mirbagheri and MR.

Deevband. The research work was proofread and supervised by MM. Mirbagheri and MR. Deevband. Clinical help was provided by M. Soleimani and A. Shahrokhi. All the authors read, modified, and approved the final version of the manuscript.

Ethical Approval

Informed Consent

Written informed consent has been obtained from the parents of patients to publish this paper.

Funding

Conflict of Interest

None

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