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PATIENTS UNDERGOING HEMISPHERECTOMY EXHIBIT CEREBELLAR REORGANISATION AND NEUROPLASTICITY

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ABSTRACT

The field of medicine was under the impression for a considerable amount of time that the brain was "hard-wired" with predetermined neural circuits, and that it remained unchanged in its structure and function We now understand that throughout a person's lifetime, the brain is constantly making adjustments and reorganizing itself through generating new neuronal connections. It is now common knowledge that the brain is intrinsically capable of altering in response to trauma, which makes it possible for at least some forms of behavioral compensation to take place.

Keyword: neuronal connections, intrinsically capable, behavioral compensation,

INTRODUCTION

In the last several decades, researchers have uncovered evidence indicating the cerebral cortex is extremely dynamic, as opposed to having a structure and function that are fixed. Neuroplasticity is the term used to describe the dynamic change that occurs in an individual's brain during the course of their life. In the second part of the 20th century, when new studies

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proved that many features of the brain remain "plastic," even into adulthood, neuroplasticity became a popular term. It enables the neurons to adapt their activity in reaction to new circumstances or to changes in their surroundings, which may occasionally result in the recovery of brain functions. It also enables the neurons to compensate for damage and sickness. Children have a greater capacity for brain plasticity than adults do, as evidenced by their superior ability to learn a second language or their capacity to recover from brain injuries or radical surgery such as hemispherectomy for epilepsy. This can be seen in children's superior ability to learn a second language than in adults.

There is evidence to suggest that neurogenesis also takes place in the adult brain, and these changes may continue to exist even far into old life. The evidence for neurogenesis is mostly confined to the hippocampus and the olfactory bulb; however, recent studies have shown that other regions of the brain, including the cerebellum, may also be involved. Applications and instances of neuroplasticity include effective improvements in individuals with amblyopia, convergence insufficiency, or stereo vision anomalies, as well as favourable results after hemispherectomy in Rasmussen encephalitis. An example of neuroplasticity that is worth noting here is a case that was published in the journal 'Neurology India' and describes a patient who had functional hemispherectomy in order to treat persistent seizures that were caused by right hemispheric cortical dysplasia. This patient had just modest weakness on the left side, with both their gross and fine motor function remaining unaffected. However, the results of an fMRI indicated that the motor function had completely switched to the normal hemisphere.

Cerebral hemispherectomy, often known as the removal of one complete hemisphere of the brain by surgical means, is a procedure that is undertaken in instances of epilepsy that is both severe and difficult to control. Surprisingly, despite post-surgical abnormalities such as hemiparesis and hemianopsia, patients are often able to restore a surprising degree of cognitive and sensorimotor function in the long term by making use of the hemisphere of the brain that was not removed during the procedure. The neuronal plasticity that underpins this functional recovery is a subject that is now being investigated in clinical neuroscience as part of ongoing research. Using task-based functional magnetic resonance imaging (fMRI), a substantial amount of neuroimaging literature has been accumulated documenting visual, motor, and language function in hemispherectomy patients.

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This literature reveals compensatory patterns of activity in the preserved hemisphere of these individuals. After such an invasive procedure, very little is known regarding the stability of large-scale functional brain networks and the extent to which they may be able to undergo rearrangement. Data from six high-functioning adults who had undergone either structural or functional hemispherectomy as children was acquired by Kliemann and colleagues using fMRI when the subjects were in a resting state. A whole or almost total removal of the afflicted hemisphere of the brain is the goal of the surgical operation known as anatomical hemispherectomy. This treatment often involves the removal of subcortical structures. A functional hemispherectomy is a process in which all connections between the afflicted hemisphere and the functioning hemisphere are severed in order to isolate the damaged hemisphere. In their research, Kliemann and his colleagues looked at six individuals. Two of those patients had had left hemispherectomy, while the other four had received right hemispherectomy.

The inclusion of two healthy control cohorts as a point of comparison was a novel aspect of the way the research was designed. The first control group consisted of six people who were comparable to the hemispherectomy patients in terms of demographic factors and who had MRI scans at the same location and with the same data gathering conditions as the hemispherectomy patients. The second control cohort included 1,482 persons who were drawn from a dataset that is freely accessible to the public and is known as the Brain Genomics Superstruct Project (GSP, https://www.neuroinfo.org/gsp/). The researchers analyzed the resting state fMRI datasets by using surface-based registration, which is a method that is more sensitive to individual anatomy. This was another one of the strengths of the study. The authors first investigated whether whole-brain parcellation derived from healthy control data could be successfully applied to hemispherectomy patients. Next, they investigated the reliability of functional connectomes derived from two separate scanning sessions from each individual. Lastly, they evaluated the similarities and differences between functional networks observed in a single hemisphere of patients and those computed from a single hemisphere. This was accomplished through a series of sophisticated analyses.

The authors began with a 7-network parcellation method that has been shown effective and is commonly used (9), and this scheme has been further subdivided to reach a finer resolution (10). The scientists discovered evidence for within-parcel homogeneity in individuals who had undergone hemispherectomy by using this technique, which resulted in 200 brain parcels

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being divided up into each hemisphere. This proof-of-principle analysis suggests that a parcellation scheme derived from people who have both of their hemispheres intact can be used to subdivide brains that have an anatomy that is significantly different from one another, such as the anatomy of people who have had hemispherectomy surgery.

Another ground-breaking aspect of the research carried out by Kliemann and his colleagues was the application of functional connectome fingerprinting (11), which was designed to evaluate the dependability of functional connectivity profiles by making use of fMRI data obtained from the same individuals on two separate occasions. According to the findings of these studies, connectome fingerprinting was effective for the majority of patients who had undergone hemispherectomy as well as control participants (5 out of 6 in both instances), as well as the majority of people who were included in the GSP dataset. This indicates that the functional connectome of the brain was consistent and discriminative across the bulk of the datasets that were investigated (i.e., it was able to identify particular people).

The comparison of within- and between-network functional connectivity with equivalent metrics collected from control participants was the primary test used to evaluate the functional network integrity of patients who had undergone hemispherectomy. Surprisingly, when several analytic approaches were used, it was shown that the within-network intrahemispheric functional connectivity of the hemispherectomy cohort and the two control cohorts were reasonably equivalent to one another. In a comparison of the functional connectedness across networks of different groups, those who had hemispherectomy showed a much greater level of connection than the two control cohorts combined. This indicates that the connection between brain parcels that belonged to different networks was greater than predicted in people who had undergone hemispherectomy. This discovery was consistent across almost all of the large-scale networks that were investigated. In patients who had hemispherectomy, the greater between-network connection result was most obvious for the somatosensory/motor and visual networks. This is an important finding.

One of the most intriguing aspects of the patients who had undergone hemispherectomy was the fact that for some of these people, the negative association that is generally shown between default mode and attention networks was significantly diminished. Finally, the authors found that global efficiency, which is defined as the average length of the inverse shortest path in a network, and modularity, which refers to the degree to which the overall network can be subdivided into groups of nodes, were both intact, and in some cases even relatively high, in patients who had undergone hemispherectomy. These findings were reached by using graph theoretical analyses.

This research is the most in-depth assessment to date of the whole-brain functional connectivity and network integrity of individuals who have had hemispherectomy. The authors explored brain network features in a rather large population of patients using state-of-the-art analytic methods and insights from network neuroscience (13,14). They then compared these measures to well-characterized samples of neurotypical persons. These individuals who have had extensive neurosurgery were found to have very little variations in their functional network connection when compared to one another, which is perhaps the most startling finding that can be drawn from this research. According to the authors' interpretation, the fact that hemispherectomy patients had stronger between-network functional connectivity reflects adaptive improvements in network integration as a compensatory technique to enhance cognitive performance.

Following up on this research, the most important issue to ask is: how does functional network remodeling enhance cognition and behavior in these individuals? The scientists did uncover some clues of connections between network measures and social responsiveness, IQ, and psychomotor function in the patients that were evaluated; but, because to the limited sample size, rigorous studies were not possible when attempting to answer this topic. Finding out how individual variations in functional network connection relate to functional outcomes in patients will be an essential part of future research.

REVIEW LITERATURE

Skeide (2010) did a meta-analysis of the studies that has been done on the subject of meditation and neuroplasticity. This line of inquiry in the research began with the hypothesis that the brain had the capability of controlling and influencing both physiological and psychological processes. Making use of the brain's capacity for change might be beneficial to a wide variety of people, including those of all ages, who are suffering from mental or physical disease, as well as those who are well. In order to determine whether or not meditation improves neuroplasticity, researchers began by analyzing a variety of factors that have, up until this point, been hypothesized to play a role in determining plasticity.

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These variables ranged from environmental factors to the levels of hormones and neurotransmitters in the brain. In this research, certain indirect evidences were investigated in order to address the questions that were posed. To begin, it seems that meditation might lessen the activity of the sympathetic nervous system, which leads to a state of calm. It has been shown that lowering one's stress levels may have both neuroprotective and neurotrophic benefits on the brain. One potential mechanism for greater plasticity is the maintenance of living neurons as well as the generation of new neurons in response to experience. It was shown that attention is connected with enhanced synchronization of neuronal activity in the parts of the brain that are responsible for representing the item that is being focused on, particularly in the gamma frequency band.

frequency. It has been shown that gamma band activity may be incorporated into plasticity, more especially in the form of long term potentiation. As a result, plasticity may be increased by the practice of meditation due to the training of attention. The ability of long-term meditators to self-induce prolonged attention may be the key factor responsible for the enhancement of plasticity brought on by meditation. Relaxation, on the other hand, is only a by-product of attention and contributes only marginally to the impact. At the same time, it is possible to conceive some applications of concentration that are not conducive to rest. In addition, we have shown that attention could be best viewed both as a tool that is engaged during meditation as well as a result, since meditation seems to strengthen attentional capacities not just during meditation but also outside of meditation. If this is the case, then instructing kids on how to meditate may not be the most effective technique to increase the students' capacity for learning. If, on the other hand, increasing one's level of relaxation while simultaneously increasing their level of concentration has a synergistic impact, then maybe meditation is especially well suited for doing this job. Even a brief session of meditation seems to have the effect of lowering stress and improving attentional skills, but these benefits may not be permanent. The findings of the studies revealed that routines or activities that entail the decrease of stress and the intentional employment of attention could increase neuroplasticity. The researchers came to the conclusion that regular meditation practice has the potential to mitigate these effects and boost plasticity and learning.

frequency. It has been shown that gamma band activity can be integrated into plasticity, particularly in the form of long term potentiation.[Citation needed] As a consequence, as a result of the training of attention that is included in the practice of meditation, plasticity may be strengthened. It is possible that the capacity of long-term meditators to self-induce extended attention is the primary component responsible for the improvement of neural plasticity brought about by meditation. On the other hand, relaxation is only a by-product of concentration and makes only a minimal contribution to the effect. At the same time, it is feasible to think of certain uses of focus that are not favorable to rest. These applications are plausible. In addition, we have demonstrated that attention can be best viewed both as a tool that is engaged during meditation and as a result of meditation, given that meditation appears to strengthen attentional capacities not only during meditation but also outside of meditation. This is because meditation seems to improve attentional capacities not only during meditation but also outside of meditation.

RESEARCH METHODOLOGY

STUDY PROTOCOL

Participants

This body of study comprised a total of 32 people who were diagnosed with CP, in addition to five toddlers and five adults who exhibited usual growth and development. Children diagnosed with cerebral palsy were given the opportunity to participate in a gross motor intervention that was accompanied by MRI scans both before and after the intervention. Children and adults who were considered to have typically developing brains were asked to complete a single MRI assessment for the purposes of enhancing the ankle dorsiflexion fMRI paradigm (Chapter 3). In Chapters 3-5, the respective findings sections each report on a different subgroup of these individuals.

Recruitment And Enrolment

Participants were considered eligible if they were able to I follow the directions for the three-step test, and (ii) they did not have any MRI contraindications (e.g., ferromagnetic implants, dental braces.). Chapters 3-5 detail the eligibility requirements that must be met in order to participate for each participant group specifically. Children who were considered to be developing normally were solicited using fliers that were put at the Holland Bloorview Kids Rehabilitation Hospital. At the Holland Bloorview Children's Hospital and the Hospital for Sick Children, researchers recruited healthy people by word of mouth (SickKids).

Two different methods were used to find children diagnosed with CP to participate in the study. Parents of potentially eligible participants who met diagnostic criteria and who were enrolled in the Child Development Program at Holland Bloorview received invitation letters in the mail. Clinicians at Holland Bloorview and two partner centers (ErinoakKids Centre for Treatment and Development, and Grandview Children's Centre) were provided information about the trial to communicate with patients who could be eligible for participation.

Parents who were interested were encouraged to get in touch with members of the research team. In each and every instance, the initial phase consisted of a preliminary screening over the phone with AJH, which was then followed by a more in-depth eligibility questionnaire (if appropriate). The second phase, which was a formal screening evaluation at Holland Bloorview, was taken by individuals who had already satisfied the basic criterion. During this appointment, a screening assessor will be present (Physiotherapist or Registered Kinesiologist)

With the Selective Control Assessment of the Lower Extremity (SCALE), the subject's capacity to unilaterally and bilaterally isolate ankle dorsiflexion was assessed (Fowler et al. 2009). In addition, the examiner looked at the candidate's capacity to do an ankle dorsiflexion task while inside of a purpose-built MRI simulator with as little head and body movement as possible. When determining whether or not a participant was eligible for the study, the researchers looked through the screening assessor's results.

Ethics

The Study Ethics Boards at Holland Bloorview, SickKids, and the University of Toronto have all looked over and given their approval to each and every one of the research procedures. The following additional study sites, when necessary, provided clearance from their respective Research Ethics or Research Advisory Committees: ErinoakKids Centre for Treatment and Development, Grandview Children's Centre, and Baycrest Health Sciences. Between Holland Bloorview and the various venues where the intervention sessions took place, Memorandums of Understanding were drafted and signed. All participants, as well as their parents or legal guardians, were asked for and given their written informed assent and agreement before the study began.

Study flow for participants with CP

Children diagnosed with CP participated in one of the three interventions described in section

2.2. Pre- and post-intervention assessments, which included neuroimaging, were conducted within ten days of the start and end of the intervention, and a clinical assessment conducted between two and six months after the intervention but without neuroimaging was carried out to evaluate long-term functional change. The flow of the study is shown in table 3.1.

Study Flow Outline

Baseline assessment	**Gross Motor Intervention**	**Post-intervention assessment (Follow-up 1)**	**Long-term assessment (Follow-up 2)**
≤10 days pre-intervention	*6-8 weeks*	*≤10 days post-intervention*	*2-6 months post-intervention*
1. Neuroimaging (1.5h) 2. Movement assessment(2.5h)	16 sessions	1. Neuroimaging (1.5h) 2. Movement assessment(2.5h)	1. Movement assessment (2.5h)

Legend: h = hour

DATA ANALYSIS

INTRODUCTION

The possible patterns of neuroplasticity are not well known, despite the fact that functional neuroplastic change may give key markers for motor skill development in children with diplegic cerebral palsy (DCP). Children who have DCP have a non-progressive brain damage that happens early in development and largely impairs the sensorimotor control of the lower limbs (Jones et al. 2007). Distal control is particularly difficult for these children to master because of the severity of their condition (Fowler et al. 2010). Interventions for children who are capable of walking on their own often concentrate on improving either gross motor coordination, balance, or muscular weakness (Palisano et al. 2012). While there is evidence of improvement in gross motor skills, the efficacy of the interventions varies, and there is no universal agreement about the best course of action (Novak et al. 2013). An knowledge of the

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functional neuroplastic shift that may improve skill development is essential, but to this day, it has been under-explored, which makes it difficult to guide therapeutic choices for gross motor disorders.

Researchers have started using cross-sectional research to map the structural, microstructural, and functional brain features of children with developmental coordination disorder (DCP). There is a wide variety of damage patterns, although the bilateral lower limb corticospinal tract (CST) projections from the primary motor cortex (M1) are often implicated. Connectivity in the CST typically occurs from one M1 hemisphere to the contralateral body side; however, in DCP, lower limb projections may link to either M1 hemisphere (Wittenberg 2009). In addition to the direct involvement of M1, defects in the macro and microstructure of the thalamocortical pathways may have an effect on the sensorimotor connection that is necessary for proper motor signaling (Hoon et al. 2009). Using resting-state functional magnetic resonance imaging (fMRI), researchers have also found evidence of an abnormally large enlargement of the sensorimotor network (Burton et al. 2009).

Because of its high spatial resolution, functional magnetic resonance imaging (fMRI) is an effective approach for understanding the motor cortex remapping and changes in activation volume (activated voxels) that may occur with improvements in motor ability (Callan and Naito 2014). For children who have hemiplegic cerebral palsy, there is some evidence to indicate that a shift toward a higher ratio of contralateral M1 activity may lead to better functional outcomes of the afflicted arm (Inguaggiato et al. 2013). Functional expansion, which is accompanied by an increase in the total activation volume, is linked to the early learning of skills (Callan and Naito 2014). As one's abilities are perfected, the amount of effort required to activate them decreases (Naito and Hirose 2014). In people who have had a stroke, a higher activation volume after training may imply that there is a possibility for continuing lower limb skill development (Dobkin et al. 2004). It is necessary to investigate laterality and amount of activation in order to identify whether or whether improvements in lower limb function are connected with neuroplastic changes in DCP (Phillips et al. 2007).

We created a task-based fMRI paradigm for ankle dorsiflexion that enables measurement of the laterality and activation volume of lower limb-linked M1 activity in children with cerebral palsy (Chapter 3). In addition, the utilization of resting-state functional magnetic resonance imaging (rsfMRI) in conjunction with task-based functional magnetic resonance imaging (fMRI) provides the opportunity to investigate alterations in interhemispheric M1 functional connectivity (FC), which may accompany activation shifts identified by task-based fMRI (Zhang et al. 2016b). Assessing the link between the prospective functional neuroplastic change and the post-intervention improvements in movement abilities is necessary in order to have an understanding of the therapeutic significance of the change. In addition, if the results of the imaging can be used to forecast the potential for motor improvements, then the interventions and training dosage may be specifically customized (Dobkin et al. 2004; Schertz et al. 2016).

The major objective of this exploratory research was to assess relationships between shifts in M1 activity and advanced motor abilities in children with DCP after they had participated in gross motor therapies. It was expected that improvements in motor competence would be related with increased contralateral activity. The secondary goals of this study were to investigate patterns of M1 activation and FC, as well as to establish if M1 activity or FC can accurately predict motor improvements at post-intervention or long-term follow-up.

METHODS

In this prospective trial, magnetic resonance imaging (MRI) and movement evaluations were carried out within a 10-day goal window both before the beginning of a gross motor intervention (the baseline) and after the conclusion of the intervention (follow-up 1). An additional evaluation was conducted between 4 and 6 months after the intervention, and it focused only on motor results (follow-up 2).

Participants

Children were included in one of the two clinical intervention studies that will be discussed further down after being recruited via local paediatric rehabilitation centers. Children were considered eligible if they met all of the following criteria: 1) they had a clinical diagnosis of spastic DCP; 2) they were classified in Levels I-II of the Gross Motor Function Classification System (GMFCS); 3) they were between the ages of 8 and 17 years old; and 4) they were able to independently dorsiflex both ankles as measured by the SCALE outcome (Fowler et al. 2009). The following were considered ineligible for the study: 1) patients with standard MRI contraindications (such as metal implants, dental braces, or those who were unable to lie supine for 30 minutes); 2) patients who had botulinum toxin injections within the last four

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months prior to study entry; 3) patients who had surgery within the last nine (muscle) or 12 months (bone); or 4) patients who had an uncontrolled seizure disorder. During the screening visit, study eligibility was confirmed, and the kid was given the opportunity to practice doing MRI activities on a simulator designed specifically for that purpose. This was done to verify that the child was capable of and willing to undergo MRI scanning.

The local institutional research ethics boards gave their clearance to proceed with this investigation. Participants and/or caregivers gave their consent or permission before the study was carried out..

Interventions

Participants were engaged in either lower extremity strength training or gross motor skill training, both of which are examples of manually administered and goal-directed therapies (agility, coordination). The Canadian Occupational Performance Measure (COPM) was used to identify baseline targets for gross motor function and abilities, and tailored programs were developed with an emphasis on achieving those goals (Canadian Association of Occupational Therapists 2014). Each of the four interventions lasted for six weeks and consisted of sixteen one-on-one sessions lasting for forty-five minutes each. The level of difficulty of the tasks was gradually raised during the course of the program.

Motor Skill Assessments

Assessments were carried out by physiotherapists who had been educated for the research but were unaware of any prior assessment scores. The Challenge was the major motor outcome, and it was an evaluation of advanced gross motor abilities (such as sprinting swiftly and weaving between pylons). This evaluation was created primarily for children who were in GMFCS Level I-II (Wright et al. 2017). The Challenge is comprised of three separate trials, each consisting of 20 different things, and is graded on a scale that ranges from 0 to 4, taking into account performance time and quality of movement. The total of the scores for each item's "best trial" is used to create the percentage scores that are presented. The six-minute walk test, also known as the 6MWT, was used to evaluate a subject's capacity for walking, with the total distance covered being recorded (Thompson et al. 2008).

Using the COPM, participant (or caregiver-proxy) objectives were determined, and the COPM's 1-10 rating scale was used to assess participant (or caregiver-proxy) performance

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(P) (Canadian Association of Occupational Therapists 2014). All of the measures have been validated with the use of children who have CP, and they have outstanding test-retest reliability (ICC values more than 0.75). The Challenge has a minimum detectable change of 4.35% (Wright, personal communication), and the 6MWT has a minimum detectable change of 61.9 (Level I) and 64.0 (Level II) meters (Thompson et al. 2008). Two points on the COPM are considered to be clinically significant (Canadian Association of Occupational Therapists 2014).

Image Acquisition

Imaging data were obtained utilizing a 3T Siemens Trio MRI scanner equipped with a 12-channel head coil at either of two locations. Each participant's pre- and post-scans were carried out at the same location throughout the whole study.

The scans were performed by MR technicians who had prior experience working with children, in conjunction with a member of the research team who was already acquainted with the kid (AJH). For the purpose of motion limitation and head stability, foam padding was used. Images such as a high-resolution T1- MPRAGE (1 mm iso; TR/TE/TI/FA=2,300/2.96/900/9) and a T2-weighted image (1.2 mm iso; TR/TE/FA=9,000/104/120) were among those that were obtained, as well as an EPI rsfMRI (3.5mm iso; TR/TE/FA= 2340/30/70; 120 TRs) and an EPI task

The participants were seen visually by direct observation made from the MRI console, and their movements were captured using an in-bore camera. During the process of acquiring structural images, a movie was played using MR-compatible headphones and either goggles or a mirror. The program known as Presentation was used to present various visual cues in conjunction with functional sequences (Neurobehavioral Systems Inc., Berkeley CA, USA). During the resting state sequence, the participants were told to maintain a neutral gaze and focus on a blank screen in front of them. The task sequence for the dorsiflexion of the ankle followed the approaches that had been published earlier (Chapter 3), and it used an event-related design that was carried out twice for each ankle. The symbol "+" served as a visual indication for a single movement of ankle dorsiflexion, while the symbol "O" denoted rest. Between the before and post scans, there was no change in the movement resistance or amplitude (5 degrees). It has been shown that the patterns of cortical activation that occur during ankle dorsiflexion in adults who have had a stroke are stable (Enzinger et al. 2009).

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Image Preprocessing

T1- and T2-weighted pictures were evaluated by a paediatric neuroradiologist who was blinded to the patient's clinical presentation in order to describe the kind of brain damage and its location. Matlab (Mathworks Inc., Natick MA, USA), FSL (www.fmrib.ox.ac.uk/fsl), FreeSurfer (https://surfer.nmr.mgh.harvard.edu/), and AFNI (https://afni.nimh.nih.gov/) were all used in the course of the fMRI data preparation procedure. Datasets were arranged in accordance with the dominant leg side, which was established by a physiotherapist assessor doing a ball kicking activity while blindfolded. After the data were adjusted for slice timing and motion, they were registered to the template, and finally, a 6-mm full width at half maximum Gaussian kernel was used to smooth the data spatially. Task datasets were baseline averaged. In the case of rsfMRI, unwanted signals were regressed, and the data was subjected to temporal filtering (0.01 Hz/0.2 Hz). In order to register data to the Montreal Neurological Institute (MNI) template, the ventricular and lesion masks that were developed in Freesurfer were imported into the FNIRT program that is available via FSL. The six parameters for the rigid body transformation were used to compute a maximum Euclidean displacement metric for each volume.

Fmri Task Data Analysis

The laterality index (LI) and the total volume of activation were the primary results of the task fMRI data, and they were computed as follows. The volumes in the dataset that have head motion of more than 5mm were censored. It was determined that datasets were usable if the following conditions were met: I the mean maximum head movement across all planes was less than 3mm; (ii) more than fifty percent of the gamma convolved stimuli were motionless; and (iii) the correlation between head motion and stimuli was less than 0.20. When the pictures were deemed to be satisfactory, the convolved task stimulus file was uploaded to the fMRI Expert Analysis Tool at FSL and used there as an explanatory variable (FEAT). The activation maps were first thresholded at $z>2.3$ with a corrected cluster significance threshold of $p=0.05$. After that, the maps were thresholded at 70% of the maximal z-score inside the bilateral lower limb M1 area of interest (ROI). The clusters contained within the ROI were chosen based on the methods that had been reported previously (Chapter 3), and then they were binarized into one mask in order to calculate: 1) volume, which is defined as the total number of active voxels; 2) area, which is defined as the

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total number of active voxels; and 3)

Rsfmri Data Analysis

The functional connectivity (FC) between bilateral M1 lower limb areas was the key rsfMRI result. rsfMRI datasets have to have more than two-thirds of their volumes with head motion of less than two millimeters. An technique to correlation that is seed-based was used. Individual seeds were expanded to their maximum size of sixty voxels, and the mean intervoxel blood oxygen level dependent (BOLD) signal time series had a Pearson's correlation value of less than 0.80. Follow-up seeds were dilated from the center of gravity of the baseline seed. Baseline seeds were dilated using common coordinates discovered based on group task data (after higher-level analysis in FEAT), and published nodes (Power et al. 2011). The pre- and post-seeds of each participant were pooled, the BOLD signal time series were averaged over all of the voxels in each seed, correlations between the seed and post-seed time courses were determined, and the results were then translated to z-scores using Fisher's z transformation. In higher-level FEAT studies, first-level FEAT pictures were merged (with the M1 seed time series serving as the explanatory variable), which allowed for the visualization of mean group activation patterns.

Statistical Design

In order to do statistical analysis, SPSS (version 24; IBM, Armonk, New York, USA) was used. In all of the studies, patients were analyzed based on their intended treatment. The data were summarized according to the outcomes, and descriptive statistics such as means and standard deviations were provided (Change 1: follow-up 1 minus pre; Change 2: follow-up 2 minus follow-up 1; Change 3: follow-up 2 minus baseline). The Shapiro-Wilk test was used in order to evaluate the normality of the data.

Paired t-tests, which assume normal distributions, as well as Wilcoxon Signed-Rank tests were used to analyze the progression of fMRI results across time (non-normal). Repeated measures analyses of variance were performed to evaluate the effects of time on motor skill outcomes, and post-hoc tests conducted with Bonferroni corrections were employed to account for the impact of multiple comparisons (p 0.017). For the modifications that did not approach statistical significance, post hoc power estimates were carried out.

Exploring the associations between fMRI (LI, volume, and FC) and motor skill tests was accomplished via the use of pairwise correlations of change scores (the main purpose) and of baseline values (Challenge, COPM, 6MWT). The Pearson correlation (r) and the Spearman rank order coefficient (rs) were used to analyze the correlations, depending on whether the data came from a normal or non-normal distribution. For the sake of this exploratory study, significant correlations were determined to exist when both $|r|>0.40$ and p0.05 (uncorrected) were present.

For the purpose of identifying fMRI predictors of Challenge change, linear regression analysis were carried out (secondary aim). The model of Challenge Change 1 used baseline fMRI measurements (LI, volume, and FC) as predictors of motor skill improvements at follow-up. These measures were taken at the beginning of the study. 1. The model of Challenge Change 2 incorporated follow-up 1 fMRI measurements as predictors of improvement or deterioration in motor abilities at follow-up as a result of the challenge. 2. The model of Challenge Change 3 used baseline fMRI measurements as potential indicators of cumulative motor skill increases from baseline to follow-up. 2. The approach for forward regression used a probability threshold of F0.05 (variable entry) and $F>0.10$ (removal).

RESULTS

Seventeen participants met study eligibility criteria (mean age 12 years, SD 2 years 11 months) and were recruited to the study. Participant and intervention characteristics are detailed in Table4.1

Participant And Intervention/Assessment Characteristics

Variable	n=17
Age (years)	Mean 12 years 0 months (SD 2 years 11 months)
Sex	6 female, 11 male
GMFCS Level	Level I n=9 Level II n=8
Lesion location/type	Periventricular leukomalacia n=7Predominantly white matter injury n=2 White matter maldevelopment (volume reduction) n=2Bilateral middle cerebral arterial infarct n=1

	Left arachnoid cyst n=1 Normal MRI n=4
Dominant side	Right n=9 Left n=8
Intervention	Strength n=5 Skill n=12

Data from 14 to 17 participants were available for each fMRI measure time point, with 13 to 14 paired (i.e., pre/post) datasets available. One follow-up scan was not completed due to dental braces, and one rsfMRI scan was not completed due to participant anxiety. All other missing datawere due to image quality in three participants, including: non-dominant ankle at baseline (n=2) and follow-up 1 (n=2); dominant ankle at follow-up 1 (n=2); and rsfMRI at follow-up 1 (n=1).

Follow-up 2 motor skill data includes 15 participants, as one participant had surgery and a second moved out of the country prior to the assessment. Table 4.2 reports mean scores for eachmeasure.

CONCLUSION

Changes in functional neuroplasticity as well as motor skills were reported in children diagnosed with HCP who underwent therapies that focused on the lower extremities. There was no association seen between the lateralization of M1 activation and motor abilities for either ankle, which suggests that children with variable degrees of CST connection may still benefit from exercising their lower extremities. It's possible that the total amount of M1 activity at baseline will be helpful for calculating the appropriate individual therapeutic dosage, which may need more time spent training for youngsters whose activation volumes are larger. Nevertheless, this is something that has to be researched with a bigger sample size. More study is needed in the future to understand the modifications that enable continuing motor progress after an intervention has been finished.

In children with Down syndrome who were able to walk independently before and after participating in gross motor training, functional neuroplasticity and gains in gross motor skills were seen. A smaller volume of activation during non-dominant ankle dorsiflexion at follow-up predicts continued movement gains at follow-up 2, according to the findings, which indicate that increased ipsilateral activity during non-dominant ankle motor cortical activation is associated with changes in motor skills. The patterns of neuroplastic change call for more research in a broader population.

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