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Resting State and Diffusion Neuroimaging Predictors of Clinical Improvements Following Constraint-Induced Movement Therapy in Children With Hemiplegic Cerebral Palsy

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Abstract
The aim was to identify neuroimaging predictors of clinical improvements following constraint-induced movement therapy. Resting state functional magnetic resonance and diffusion tensor imaging data was acquired in 7 children with hemiplegic cerebral palsy. Clinical and magnetic resonance imaging (MRI) data were acquired at baseline and 1 month later following a 3-week constraint therapy regimen. A more negative baseline laterality index characterizing an atypical unilateral sensorimotor resting state network significantly correlated with an improvement in the Canadian Occupational Performance Measure score ($r = -0.81$, $P = .03$). A more unilateral network with decreased activity in the affected hemisphere was associated with greater improvements in clinical scores. Higher mean diffusivity in the posterior limb of the internal capsule of the affect tract correlated significantly with improvements in the Jebsen-Taylor score ($r = -0.83$, $P = .02$). Children with more compromised networks and tracts improved the most following constraint therapy.

Cerebral palsy is a group of disorders affecting the development of movement and posture caused by a non-progressive injury to the developing brain prenatally or in early life.[1] Hemiplegic cerebral palsy is a common subtype of cerebral palsy and is characterized by unilateral involvement with impairments in the arm and/or leg.[2-4] Cortical and/or subcortical lesions caused by a middle cerebral artery stroke, asymmetrical periventricular leukomalacia, or intraventricular hemorrhages are found within motor areas in the hemisphere contralateral to the affected limb.[5] Individuals with hemiplegic cerebral palsy affecting the upper extremity experience weak grasping ability, difficulty performing intricate movements, hypertonia, decreased selective motor control, and altered proprioception.[1] Children may exhibit learned non-use wherein the hemiplegic limb is further inhibited from normal functional development[6] and executing bimanual activities.[7,8]

Constraint-induced movement therapy has the most convincing clinical evidence for improving sensorimotor function in children with hemiplegic cerebral palsy.[9,10] Constraint therapy directly attempts to combat learned non-use by physically restraining the unaffected arm, thereby forcing the individual to repetitively use the hemiplegic limb.[11,12] Initially demonstrated by Taub et al[6] in primate studies, this therapy has been effective in improving hand function in both stroke and cerebral palsy and has also been linked with evidence of

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Table 1. Subject Demographic Details and Individual Magnetic Resonance Imaging (MRI) and Clinical Scores.

Participant No.	1	2	3	4	5	6	7
Sex	M	M	F	F	M	M	M
Age	13	12	11	6	15	14	11
Affected Hemisphere	L	R	L	R	R	R	R
Injury Pattern	MCA	MCA	MCA	IVH[a]	PVL[a]	PVL	PVL[b]
Lesion Volume (mL)	57.94	5.91	8.94	81.27	79.54	10.37	1.94
Primary lesion location (C = cortical, S = subcortical)	C and S	S	C and S	C and S	C and S	S	S
Laterality index based on the number of active voxels with a cluster threshold	−0.99	−0.25	−0.49	−0.31	−1.00	−0.09	−0.31
Fraction anisotropy in the PLIC of the affected hemisphere	0.24	0.44	0.32	0.38	0.30	0.32	0.38
Mean diffusivity in the PLIC of the affected hemisphere (10^{-3})	1.3	0.81	0.84	0.88	0.97	0.89	0.79
Baseline QUEST	65.32	83.82	65.7	79.1	67.59	82.49	75.62
1-Month QUEST	78.72	88.45	78.51	81.49	71.05	88.29	90.74
Baseline COPM	3.3	3	1	1	2.5	7	5.67
1-Month COPM	9	6.3	5	5.7	8.5	6.5	8
Baseline JTTHF (s)	28	13.88	120	27	13.72	5.91	6.56
1-Month JTTHF (s)	10	7.38	120	20	9.59	7.1	5.31

Abbreviations: COPM, Canadian Occupational Performance Measure; IVH, intraventricular hemorrhage; JTTHF, Jebsen-Taylor Test of Hand Function (lifting large but light objects task); MCA, middle cerebral artery infarct; PLIC, posterior limb of the internal capsule; PVL, periventricular leukomalacia; QUEST, Quality of Upper Extremity Skills Test.
[a]With porencephaly.
[b]With periventricular germinal matrix injury.

neuroplasticity.[13] However, not all children with hemiplegic cerebral palsy experience success with this intensive and often-times frustrating treatment.[14]

Recent studies have identified poorer baseline hand function as predictors of a positive response to constraint therapy,[8,15] although possible resting state functional magnetic resonance imaging (MRI) predictors for this particular subject group have not been explored. Previous functional MRI studies of individuals with cerebral palsy treated with constraint therapy have concentrated on task-related activation experiments.[15,16] During hemiplegic hand movement, activation often occurs in the contralesional (opposite side of the lesion) hemisphere, though after therapy the affected hemisphere activity variably increases.[15,16] Task-based functional MRI has several challenges associated with it, including motion artifacts related to the motor task, inconsistent performance, mirror movements or the ability of the individual to perform the task at all.[17] Resting state functional MRI and diffusion tensor imaging are acquired in the absence of a task and allow the investigator to explore global network organization and white matter integrity.[17]

Fractional anisotropy and mean diffusivity measures quantify the degree of anisotropy (which is related to axon myelination, density, and integrity[18]) and magnitude of water diffusion, respectively. Recovery of adults with stroke after constraint therapy has been predicted using resting state interhemispheric connectivity.[19] Diffusion analysis of the corticospinal tract has also revealed a relationship between the fractional anisotropy of the tract and a positive clinical change in adults with hemiplegia secondary to an acquired stroke[20]; however, several recent reports in children have not associated corticospinal tract organization and integrity with the ability to benefit from constraint-induced movement therapy.[21,22]

In this study, we investigate baseline neuroimaging characteristics related to clinical improvements following constraint therapy in children with congenital hemiplegic cerebral palsy using resting state functional MRI and diffusion tensor imaging. We compare the clinical changes with baseline MRI data to determine potential neuroimaging predictors of improved arm functionality after constraint therapy.

Methods

Participants

Fourteen individuals diagnosed with hemiplegic cerebral palsy (hemiplegia) (all Gross Motor Function Classification System and Manual Ability Classification System Level I) as a result of cortical or subcortical injury and between the ages of 6 and 18 years with the ability to understand and participate in the treatment were originally recruited for this study from Holland Bloorview Kids Rehabilitation Hospital and McMaster Children's Hospital. They had to be able to cooperate, understand, and follow instructions for the MRI portion with the ability to remain still for about 45 minutes. The participants had no previous constraint therapy within 9 months of the study, and no botulinum toxin upper limb injections within 6 months of the study. Three of these individuals did not participate in the MRI portion of the study for various reasons (braces artifact, afraid to enter the MRI, parents were not interested in the MRI sessions), and 4 were not used due to excessive motion. The demographic and clinical descriptions are summarized in Table 1.

Study Design and Clinical Evaluation

A 3-week constraint therapy protocol was administered with the child wearing a nonremovable below-elbow cast on the non-hemiplegic limb for the first week (24 hours per day for 7 days) followed by a 2-week standardized constraint therapy camp, "Hand2Hand,"

developed at Holland Bloorview Kids Rehabilitation Hospital where the children wore a removable cast for the majority of camp-time in the first week and for 1 hour a day in the second week of camp. The children worked with an occupational therapist in the camp for 4 hours a day for 5 days per week (totaling 40 hours of camp intervention) and initially concentrated on unilateral activities with the hemiplegic hand, and added bilateral activities during the second week. They were encouraged to do 1 hour of "homework" each night replicating camp activities learned that day.

The children in this study were clinically evaluated 1 to 4 days before constraint therapy and at 1 month (+/–1 week) after baseline following the constraint-induced movement therapy. Individualized performance outcomes (Canadian Occupational Performance Measure), functional capacity (Quality of Upper Extremity Skills Test), and hemiplegic hand efficiency (Jebsen-Taylor task) were used to evaluate subjects.[23] The primary outcome, Canadian Occupational Performance Measure, focuses on individualized goals based on the participants' ability to perform 3 self-identified daily tasks. The Quality of Upper Extremity Skills Test is a standard set of tests assessing dissociated movements, grasp, extension, and weight bearing with the hemiplegic limb.[24] The total Quality of Upper Extremity Skills Test score reflects the average of all sections. The Jebsen-Taylor task with the hemiplegic hand moving large, but light, objects was identified a priori by the occupational therapists as being the most sensitive measure of functionality changes in the Jebsen-Taylor battery and this subtest is reported in the Results section. There was a 2-minute limit set per Jebsen-Taylor task. Change scores were calculated by subtracting baseline from the 1-month follow-up score. Clinically relevant changes were also examined on a group and individual basis for Canadian Occupational Performance Measure and Quality of Upper Extremity Skills Test scores, defined as an increase in 2 and 3 points, respectively.

MRI Analysis

The MRI protocol is detailed in Supplementary Information. A single investigator blinded to any clinical information or results performed all analyses. Resting state functional MRI data were only included if mean relative displacement was less than 0.55[25] and maximum displacement was less than 3 mm. A sample resting state functional MRI volume is shown in Figure 1C. The imaging data was preprocessed using the Functional Magnetic Resonance Imaging of the Brain Software Library (FSL) (http://www.fmrib.ox.ac.uk/fsl). Functional data were preprocessed using the functional MRI Expert Analysis Tool using the standard steps: brain extraction, motion correction with a Linear Image Registration Tool, 5 mm spatial smoothing, and low- and high-pass filtering (0.01-0.1 Hz) and transformation into standard space. Denoising was performed using Multivariate Exploratory Linear Optimized Decomposition into Independent Components, with 20 components per single session results from which noisy components were removed from the data.

The preprocessed functional data were then analyzed to identify the sensorimotor network using 2 different techniques: independent component analysis and a seed-based analysis. Temporally concatenated independent component analysis was used on the cleaned data to identify the average sensorimotor resting state network per subject. Dual regression algorithms were used to back-reconstruct a resting state sensorimotor network for each session. Both this network and the same network with a minimum cluster size threshold of 200 voxels were analyzed.

Before carrying out a seed-based analysis, further motion correction was applied using the "fsl_motion_outliers" tool. Volumes with large motion were detected and used to create a confound matrix that could then be used within the general linear model to remove the effect of these time points on the seed-based analysis, without compromising statistics, temporal filtering, or correlation algorithms. A region of interest was chosen from independent component-derived network motor areas in the contralesional hemisphere. The time course from this region was extracted and correlated with the rest of the brain on a voxel-wise basis to once again visualize the sensorimotor resting state network and its connectivity patterns before constraint therapy.

Laterality indices were calculated from both the independent component analysis and seed-based network results. The general laterality index (LI) equation used is:

$$LI = \frac{[Affected\ hemisphere\ data - Contralesional\ data]}{[Affected\ hemisphere\ data + Contralesional\ data]},$$

where the term *data* refers to the sensorimotor resting state network organization based on (1) the number of active (above z-threshold) voxels, (2) the average signal intensity, or (3) the average z-statistic within motor areas defined using the Harvard-Oxford Cortical Structural Atlas. A negative laterality index would indicate a bias toward the contralesional hemisphere or a more unilateral network because of the cortical and subcortical damage, whereas a laterality index approaching 0 would indicate a bilateral network pattern as seen in healthy subjects.[26]

Regions of interest were chosen from the right and left primary sensorimotor areas found in the temporally concatenated independent sensorimotor component and these time courses were correlated with each other. The standard deviation of these time series was calculated as an estimation of signal amplitude, and a laterality index based on these standard deviations was considered as a possible predictor variable.

All diffusion analysis was completed using the Diffusion Toolbox. Diffusion-weighted data were first eddy current corrected. The toolbox was then used to fit diffusion tensors to the eddy current corrected data, as well as creating fractional anisotropy and mean diffusivity maps. Average fractional anisotropy and mean diffusivity values were taken from the entire lesion volume in the affected hemisphere and at 3 points along the right and left corticospinal tracts, which were found using the Johns Hopkins University White-Matter Tractography Atlas and confirmed with the T2-weighted anatomical image. These 3 areas of interest include the pons, midbrain, and the posterior limb of the internal capsule, shown in Figure 1A.

Statistical Analysis

All analyses were performed using IBM's Statistical Product and Service Solutions (SPSS) (version 21) software. All variables were tested for skew and kurtosis using a Shapiro-Wilk test of normality, and with a P value > .05 parametric tests were used. Clinical outcome scores at baseline and postconstraint therapy were compared using a paired samples t test. The fractional anisotropy and mean diffusivity values in both corticospinal tracts were also compared this way. A bivariate correlation analysis using the Pearson correlation coefficient was applied to all baseline MRI data and clinical change scores. MRI predictors were identified as significant with a P value less than .05 after bootstrapping with 1000 samples.
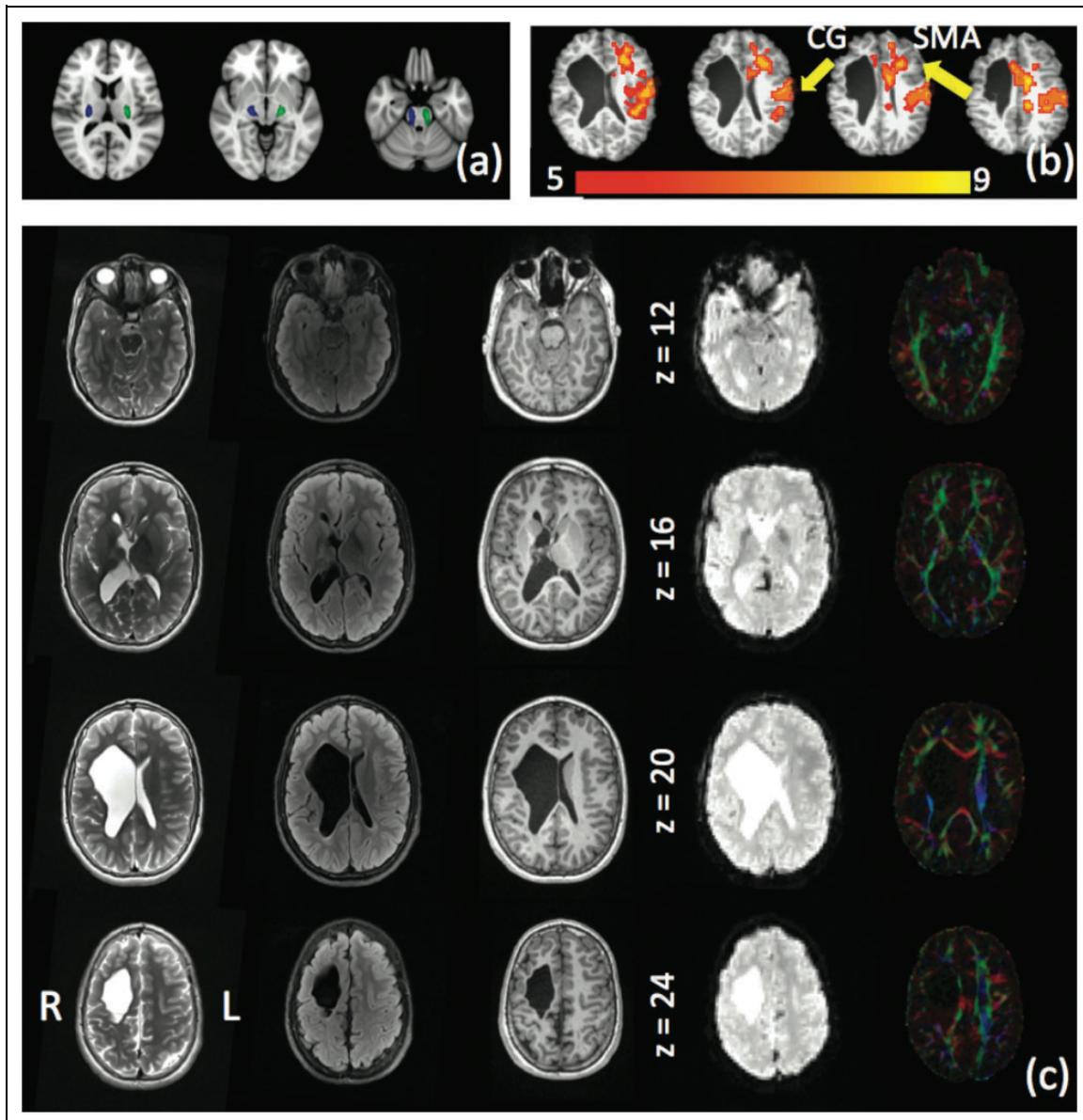
Figure 1. All images shown with radiologic convention. (A) Three diffusion regions of interest, from left to right: posterior limb of the internal capsule, midbrain, and pons along the corticospinal tract, overlaid on a standard space image. (B) A representative subject's independent component analysis derived sensorimotor resting state network at baseline colored by z-statistic according to color scale shown (CG, pre and post central gyrus, SMA, supplementary motor area). (C) From left to right column, the same representative subject's anatomical (turbo spin-echo, fluid suppression, and magnetization-prepared rapid acquisition gradient echo sequences), functional MRI volume, and diffusion fractional anisotropy color map shown on the same 4 axial planes.

Results

Clinical Results

Individual clinical results are reported in Table 1 and group results are given in Figure 2A, with error bars representing the standard error of the mean. Almost all individuals demonstrated clinically relevant improvements after constraint therapy according to an improvement of at least 3 points in the Quality of Upper Extremity Skills Test scores (7/7), an improvement of at least 2 points in the Canadian

Occupational Performance Measure average performance scores (6/7), and shortened time to complete the identified Jebsen-Taylor task (5/7). Qualities of Upper Extremity Skills Test scores on average improved by a clinically relevant amount, from a mean (and standard deviation) of 74.23 (7.98) to 82.46 (7.06), and were statistically improved ($P = .007$). Similarly, Canadian Occupational Performance Measures scores improved from 2.92 (2.02) to 6.67 (1.51) and were statistically significant ($P = .004$). Though most individuals did take less time to complete the Jebsen-Taylor

lifting a large but light object task after constraint therapy, there was a wide range of scores rendering only a trend toward significant results ($P = .08$), from 295 (237) seconds to 263 (241) seconds.

Anatomical Images

The fluid suppression anatomical image (Figure 3) had an ideal contrast for identifying the lesion manually. Primary lesion location and approximate lesion volumes are reported in Table 1 but were not correlated with any clinical changes. The T2-weighted turbo spin-echo image was useful for registration and confirming the 3 regions of interest along the right and left corticospinal tract (Figure 1A).

Sensorimotor Network Organization

Although the seed-based and independent component analysis rendered similar results, in general independent component analysis results were preferred because they were less affected by motion and seed placement was not a factor.[17] An example of an independent component–derived sensorimotor network is shown in Figure 1B.

All subjects except subject number 6 had sensorimotor resting state networks with a preference to the contralesional hemisphere with little to no involvement from the affected hemisphere. This organization was determined through laterality indices approaching –1, whereas subject 6 had a laterality index of –0.09, indicating more equal contributions from both hemispheres.

Resting State Functional MRI Predictors

Baseline laterality indices based on the number of voxels in the sensorimotor resting state network above a z-threshold of 5 were highly correlated with clinical improvements. All predictor relationships are reported in Table 2 along with the Pearson correlation coefficient and significance of the relationship.

Specifically, a negative laterality index based on activated voxels correlated with improvements in the Canadian Occupational Performance Measure score and time to complete the Jebsen-Taylor task. The same laterality index based on activated voxels with a cluster threshold applied rendered significant results when correlated with the positive change in Canadian Occupational Performance Measure score, as shown in Figure 2B. A negative laterality index based on signal intensity of the sensorimotor resting state network derived from the seed-based analysis was significantly correlated with an improvement in Quality of Upper Extremity Skills Test scores. Lower connectivity between the contralesional and affected hemisphere's motor areas were related to improvements in the Jebsen-Taylor task. Finally, a more negative laterality index based on the standard deviations was also related to positive change in the Quality of Upper Extremity Skills Test score.
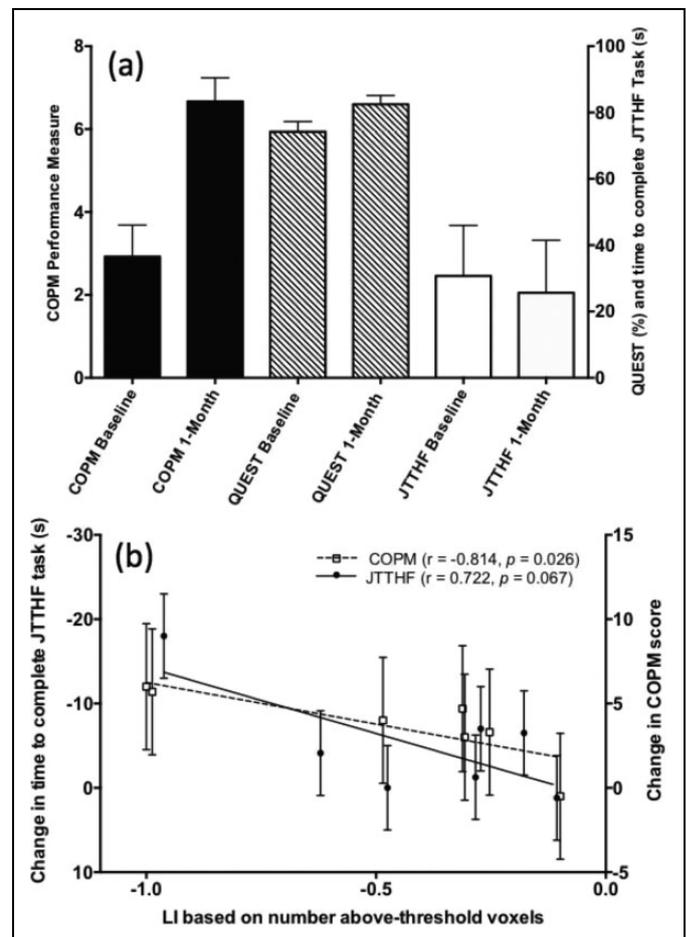
Figure 2. (A) Average Canadian Occupational Performance Measure (COPM), Quality of Upper Extremity Skills Test (QUEST) rated out of 100 (ie, %), and time to complete Jebsen-Taylor (JTTHF) lifting a large but light object task scores before and after constraint therapy, with error bars depicting the standard error of the mean. (B) The relationship between the change in COPM and JTTHF scores before and after constraint therapy as a function of a baseline resting state laterality index (LI) based on the number of above-threshold voxels, with a line of best fit shown and error bars representing the standard deviation.

Diffusion of the Corticospinal Tract

The baseline fractional anisotropy in the affected tract's midbrain region of interest was 0.34 (0.057) and was significantly lower compared to the contralesional tract with 0.40 (0.067), ($t = 2.97$, $P = .01$), whereas the average affected hemisphere's mean diffusivity was 0.0013 mm^2/s (0.00034) and was significantly higher compared to the contralesional tract, with 0.00084 mm^2/s (0.00010) ($t = 2.21$, $P = .03$). A representative fractional anisotropy color map is shown in Figure 1C. Higher mean diffusivity in the affected posterior limb of the internal capsule of the corticospinal tract was significantly correlated with an improvement in the time to complete the Jebsen-Taylor task ($r = –0.83$, $P = .02$).
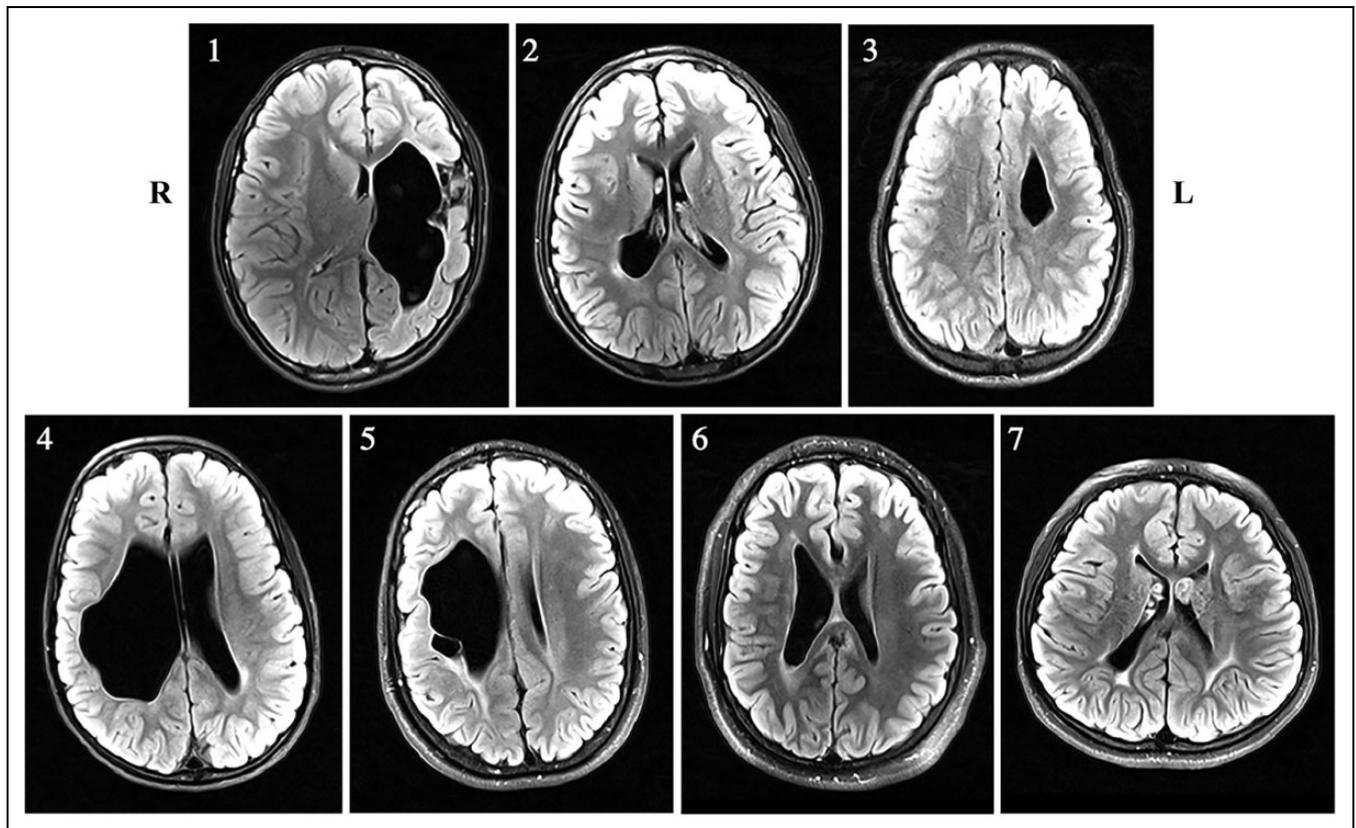
Figure 3. Anatomical fluid attenuated inversion recovery sequence images for each of the 7 participants. All images are shown with radiologic convention and these single slices display the maximum lesion volume. Individual injury patterns are detailed in Table 1.

Discussion

This study aimed to identify MRI resting state and diffusion imaging predictors of improved functionality following constraint therapy in individuals with congenital hemiplegic cerebral palsy. Average and individual clinical scores taken before and after constraint therapy indicate that participants improved various aspects of hand function following the therapy, as shown in many previous studies of constraint therapy.[10] These standard clinical measures complement each other well, together providing customized subject-specific data based on personal goals and reliable quantitative measures sensitive to hemiplegic hand functional capability and efficiency changes after therapy.

Typical sensorimotor resting state networks are fairly symmetrical and bilateral.[26] In individuals with hemiplegic cerebral palsy because of the cortical and/or subcortical damage in motor related areas and possible learned non-use, we found that networks were asymmetric, except for 1 subject. The sensorimotor resting state network derived through independent component analysis was found to have altered connectivity patterns at baseline, with asymmetric correlated activity within motor areas in the unaffected hemisphere, as well as the supplementary motor area. This asymmetric unilateral sensorimotor network organization was observed in most subjects, regardless of lesion volume, suggesting that injury location rather than size is more relevant to motor impairment.[21]

Our novel finding is that subjects with a resting state network deemed more asymmetric according to laterality indices based on these altered connectivity patterns tended to improve the most according to both the change in Canadian Occupational Performance Measure score and the time to complete the Jebsen-Taylor task, whereas subjects with more symmetric and bilateral baseline sensorimotor network organization showed the least improvement. The mechanism of constraint therapy may be optimally linked with the opportunity to restore bilateral connectivity. Although the nature of resting state functional MRI makes it difficult to uncover the underlying neurophysiology,[27] there are a few hypotheses we can develop from the data. Initial lower correlations in the resting state functional MRI time series between contralesional and affected motor areas were linked with better outcomes after therapy. Stunted connectivity could be due to the absence of structural connections or abnormal communication between the 2 areas. The laterality index based on signal amplitudes also indicates a preference to the contralesional hemisphere, with lower, possibly inhibited signal fluctuations being related to better outcomes. These unilateral baseline networks could have existing physical connections to the affected hemisphere; however, they are being strongly inhibited by the contralesional side. Stroke patients often have increased interhemispheric inhibition from the contralesional to the affected hemisphere, which is related to the degree of motor impairment,[28] and

Table 2. Predictor Relationships Between Baseline Magnetic Resonance Imaging (MRI) Data and Clinical Change Scores.[a]

Baseline MRI predictor	Clinical Change	Correlation coefficient (r)	Significance (P)
LI based on the number of active voxels	COPM	−0.75	.05[a]
	JTTHF	0.72	.07
	QUEST	−0.38	.4
LI based on the number of active voxels with a cluster threshold	COPM	−0.81	.03[a]
	JTTHF	0.60	.2
	QUEST	−0.15	.7
LI based on signal intensities (seed-based analysis)	COPM	−0.27	.6
	JTTHF	−0.14	.7
	QUEST	−0.79	.03[a]
Mean diffusivity in the affected PLIC	COPM	0.46	.3
	JTTHF	−0.83	.02[a]
	QUEST	0.21	.7
Correlation between the contralesional and affected hemispheres	COPM	−0.09	.9
	JTTHF	0.79	.03[a]
	QUEST	−0.28	.6
LI based on the standard deviations	COPM	−0.58	.2
	JTTHF	0.20	.7
	QUEST	−0.73	.06

Abbreviations: COPM, Canadian Occupational Performance Measure; JTTHF, Jebsen-Taylor Tests of Hand Function lifting a large but light object task; LI, laterality index; PLIC, posterior limb of the internal capsule; QUEST, Quality of Upper Extremity Skills Test.
[a]Significant relationships.

constraint therapy may improve motor function by releasing this inhibition.[29] Our predictors indicate that subjects who can take advantage of this mechanism may benefit the most. The change in Quality of Upper Extremity Skills Test scores did not significantly correlate with this particular resting state predictor. This may be secondary to a ceiling effect, as many subjects had high Quality of Upper Extremity Skills Test baseline scores with little room to improve. However, a seed-based laterality index of signal intensity was related to larger changes in the Quality of Upper Extremity Skills Test score, supporting our other predictors.

The diffusion results show that the affected corticospinal tract consistently had decreased fractional anisotropy and increased mean diffusivity values along all 3 regions of interest compared to the contralesional corticospinal tract, which agrees with previously published studies.[20,30,31] Less favorable MRI baseline data with increased mean diffusivity in the affected corticospinal tract (indicating more damage) was predictive of improved individualized performance and efficiency with the hemiplegic arm following constraint therapy. The resting state and diffusion predictors both indicate that subjects with more compromised networks and tracts improve the most after constraint therapy.

The results of this case series have to be interpreted while considering the studies limitations. Sample size was small and

consisted of a high-performing group of recruited participants (according to baseline Quality of Upper Extremity Skills Test scores). With a small group size, outliers in the data could have an influence on the outcomes. These predictors may only be applicable to a certain range of baseline clinical scores. Further studies of subject groups with a larger range of baseline clinical scores will be needed to identify a relationship that includes clinical and MRI baseline predictors of a positive response to constraint therapy. Resting state functional MRI and diffusion tensor imaging are global acquisitions that could be incorporated into current scanning regimes for this subject group and require nothing but stillness from the participant, which is vastly easier to implement compared to task-based functional MRI studies, particularly in children. As further research elucidates the strength of resting state functional MRI and diffusion tensor imaging's predictive value in studies of larger samples, they may become useful clinical tools when determining if constraint therapy is an appropriate treatment option for individuals with hemiplegic cerebral palsy.

Author Contributions

DF, RM, JWG, CC, and RSM, who all aided in subject recruitment, designed this study. Acquisition was implemented by DF, LS, CC, and RSM. KM performed all data and statistical analysis, with input on the interpretation from DF, LS, and RSM. KM wrote the article with critical revisions from all authors.

Declaration of Conflicting Interests

Funding

Ethical Approval

Research ethics approval was obtained from The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB), Holland Bloorview Research Ethics Board, and Hamilton Integrated Research Ethics Board (HIREB) and informed consent and assent were obtained; approval number 18818.

Supplementary Material

The online appendices are available at http://jcn.sagepub.com/supplemental

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