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Functional connectivity of sensorimotor network is enhanced in spastic diplegic cerebral palsy: A multimodal study using fMRI and MEG

Jaakko Vallinoja [a,*], Timo Nurmi [a,b], Julia Jaatela [a], Vincent Wens [e,h], Mathieu Bourguignon [e,f,g], Helena Mäenpää [d], Harri Piitulainen [a,b,c]

[a] Department of Neuroscience and Biomedical Engineering, Aalto University School of Science, P.O. BOX 12200, 00076 AALTO Espoo, Finland
[b] Faculty of Sport and Health Sciences, University of Jyväskylä, P.O. BOX 35, FI-40014 Jyväskylä, Finland
[c] Aalto NeuroImaging, Aalto University School of Science, Espoo, Finland
[d] Department of Child Neurology, New Children's Hospital, University of Helsinki and Helsinki University Hospital, FI-00029 Helsinki, Finland
[e] Laboratoire de Neuroanatomie et Neuroimagerie Translationnelles (LN^2T), UNI – ULB Neuroscience Institute, Université Libre de Bruxelles (ULB), Brussels, Belgium
[f] Laboratory of Neurophysiology and Movement Biomechanics, UNI – ULB Neuroscience Institute, Université Libre de Bruxelles (ULB), 1070 Brussels, Belgium
[g] BCBL, Basque Center on Cognition, Brain and Language, 20009 San Sebastian, Spain
[h] Department of Translational Neuroimaging, HUB — Hôpital Erasme, Brussels, Belgium

HIGHLIGHTS

- Diplegic cerebral palsy is associated with enhanced functional connectivity in the sensorimotor networks.
- In typically developed subjects frontoparietal connectivity in beta range correlates with kinaesthesia performance.
- fMRI and MEG both show enhanced connectivity in cerebral palsy group, but the affected regions are different.

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ABSTRACT

Objective: To assess the effects to functional connectivity (FC) caused by lesions related to spastic diplegic cerebral palsy (CP) in children and adolescents using multiple imaging modalities.
Methods: We used resting state magnetoencephalography (MEG) envelope signals in alpha, beta and gamma ranges and resting state functional magnetic resonance imaging (fMRI) signals to quantify FC between selected sensorimotor regions of interest (ROIs) in 11 adolescents with spastic diplegic cerebral palsy and 24 typically developing controls. Motor performance of the hands was quantified with gross motor, fine motor and kinesthesia tests.
Results: In fMRI, participants with CP showed enhanced FC within posterior parietal regions; in MEG, they showed enhanced interhemispheric FC between sensorimotor regions and posterior parietal regions both in alpha and lower beta bands. There was a correlation between the kinesthesia score and frontoparietal connectivity in the control population.
Conclusions: CP is associated with enhanced FC in sensorimotor network. This difference is not correlated with hand coordination performance. The effect of the lesion is likely not fully captured by temporal correlation of ROI signals.
Significance: Brain lesions can show as increased temporal correlation of activity between remote brain areas. We suggest this effect is likely separate from typical physiological correlates of functional connectivity.

1. Introduction

Cerebral palsy (CP) is a movement disorder caused by abnormal development or damage to the brain during the fetal period or shortly after birth (Rosenbaum et al., 2007). It is one of the most common causes of disability in early childhood, affecting approximately two children per 1000 live births (Oskoui et al., 2013). CP is a non-progressive neurological disorder, but it may hinder the normal development of the musculoskeletal system that can cause, e.g., increased mobility impairments throughout the lifespan (Jahnsen et al., 2004). CP encompasses a heterogenous group of

* Corresponding author.
E-mail address: jaakko.vallinoja@aalto.fi (J. Vallinoja).

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disorders. Spastic CP is by far the most common type (Johnson, 2002), characterized by increased muscle tone and hyperreflexia. Other less common types are dyskinetic CP characterized by choreo-athetosis (involuntary movements) and/or dystonia, and ataxic CP characterized by loss of muscle coordination, tremors, and low muscle tone (Cans et al., 2007). CP is also commonly classified according to the distribution of symptoms in the limbs. Hemiplegia refers to unilateral symptoms and diplegia/tetraplegia to bilateral symptoms (for analysis of these terms see Colver and Sethumadhavan, 2003; Minear, 1956).

The heterogenous symptoms under CP arise from the wide variety of the underlying cerebral lesions and their specific effects. These lesions can be roughly divided into white matter lesions, basal ganglia and thalamic lesions, cerebellar lesions, and cortical lesions. Cerebellar damage typically causes ataxic symptoms; dyskinetic and choreoathetotic symptoms are often associated with damage to basal ganglia and/or thalamus (Hou et al., 2006). White matter lesions are common to all CP types and cortical gray matter lesions are typical in unilateral CP types (Korzeniewski et al., 2008). Spasticity symptoms usually arise from cortical or white matter lesions. Hemiplegic spasticity symptoms usually result from focal perinatal injuries or infarctions in vascular distribution. In diplegic spastic CP, by far the most common underlying lesion is a white matter injury, often ischemia around the lateral ventricles (periventricular leukomalacia, PVL), which is common with children born preterm or with a prolonged hypoxic-ischemic event (McManus et al., 2006; Rezaie and Dean, 2002).

One systematic method to study large scale functional differences caused by brain lesions is to quantify changes to functional connectivity (FC) in the brain. In short, the FC can be defined as the temporal dependency (usually correlation or coherence) of neuronal activity between anatomically separate brain regions. When studying FC, the brain is examined as a large-scale network of interacting functional components (Aertsen et al., 1989; Friston et al., 1993). CP has been shown to influence cortical functional connectivity, but the observations and used methodology are variable. Using functional magnetic resonance imaging (fMRI), the FC within the sensorimotor network has been reported to be enhanced in CP by some studies (Burton et al., 2009; Mu et al., 2018), while others reported the opposite (Qin et al., 2018). To our knowledge, there are no direct studies on FC alterations in CP using magnetoencephalography (MEG). However, increased connectivity in MEG has been found in preterm children (Kozhemiako et al., 2019). Furthermore, some MEG studies have found impairments of functional lateralization (Guo et al., 2012) and increased beta power (Sajedi et al., 2013) in children with CP. A better understanding of what kinds of FC changes are shown with different methods and how the measures correlate with the sensorimotor symptoms in CP would improve our understanding of the fundamental processing of the sensorimotor system.

FC is often examined using resting state measurements where the primary source of activity is spontaneous rather than driven by an external stimulus (Damoiseaux et al., 2006; Gusnard and Raichle, 2001). Resting state FC is commonly measured using fMRI which measures the blood oxygen level dependent signal (BOLD) which is an indirect measure of neural activity through hemodynamic response (Logothetis et al., 2001). Resting state fMRI is a well-established method that has been widely used for decades. The use of MEG to examine the resting state functional networks is far less common compared to fMRI, even though MEG can be viewed as a more direct measure of neural activity than fMRI and can unveil finer temporal and spectral aspects. MEG measures directly the magnetic fields generated by post synaptic electric activity of neuron populations (Hämäläinen et al., 1993). However, MEG is more limited than fMRI regarding its spatial resolution, due to challenges in the localization and separation of neural sources. The MEG signal in each sensor is a mixture of all cortical neural sources and it is impossible to perfectly decompose these mixtures into the original sources (Hämäläinen et al., 1993; Hämäläinen and Ilmoniemi, 1994). As such, MEG images of neural activity are typically blurry, and this leads to artefactual connectivity estimation (Wens, 2015). Several methods have been developed to mitigate this difficulty (Brookes et al., 2012; Colclough et al., 2015; Hipp et al., 2012; Wens et al., 2015). Taken in conjunction with the power envelope correlation technique to quantify FC, resting state MEG has successfully identified similar cortical functional network structures as fMRI (Brookes et al., 2011a; De Pasquale et al., 2010; Hipp et al., 2012; Sjøgård et al., 2019; Wens, 2015), although reproducibility differs between MEG and fMRI (for a review of methods see Colclough et al., 2016).

In the present study, our primary aim was to examine the resting state FC in the sensorimotor cortices in spastic diplegic children and adolescents with CP in comparison to their healthy peers. Previous results on FC in CP are partly contradictory and there is very limited evidence from MEG studies. We aim to provide novel information about brain basis of spastic diplegic CP, the effects FC could have on the motor impairments. Our other objective is to compare MEG and fMRI to further examine how different imaging modalities converge or if they measure different effects. This information is relevant for future interpretation of FC results. To that effect, we utilized a similar resting state design in both MEG and fMRI recordings and aimed to comprehensively clarify how CP alters FC by comparing MEG power envelope and fMRI correlation measures. Lastly, to improve the understanding of the physiological implication of FC, we examined the correlation between MEG and fMRI connectivity measures and hand fine and gross motor skills.

2. Materials and methods

2.1. Participants

In total 11 children and adolescents with spastic diplegic CP and 27 typically developing (TD) peers were recruited (see Table 1 for further details). The gross motor skill of the patients was classified to level I–II in the Gross Motor Function Classification System, meaning the participants had the ability to walk independently without assistive devices but with some impairments in the ability to perform gross motor skills such as running and jumping (Rosenbaum et al., 2008). Their manual ability was level I–II in the manual ability classification system, meaning that they could handle most objects independently in daily activities, albeit possibly with reduced quality and speed (Eliasson et al., 2006). Participants had no known cognitive, co-operative, hearing or visual deficiencies (that cannot be corrected using spectacles). We also excluded participants with medication that is known to affect motor performance. The patients were recruited from the rehabilitation unit of Childreńs Hospital, Helsinki University Hospital and by advertising via a patient organization. The study was approved by the ethics committee of Helsinki University Hospital (HUS/2318/2016) and was conducted in accordance with the Helsinki Declaration. All volunteers and their guardians gave written informed consent prior to participation in the study.

Due to complications during measurement sessions (e.g., discomfort or fear of entering the MRI scanner) some participants did not finish all the functional or structural measurements. Some data also had to be discarded due to quality issues (excessive noise and artefacts in fMRI or MEG, failed head position tracking in MEG). Out of the 11 participants in the CP group, 9 patients were successfully recorded in MEG and 9 in fMRI, and 7 successfully in both (see Table 1). Participants' handedness was investigated using Edinburgh Handedness Inventory (Oldfield, 1971). Table 2 shows

Table 2
Information about lesion in the CP group.

Subject	Type of lesion	MRI description	Included in analysis
CP01	PVL	White matter reduction around ventricles and thalamus	fMRI, MEG
CP02	PVL	PVL	MEG
CP03	ICH, IVH	Bilateral white matter lesion in corona radiata	fMRI, MEG
CP04	HIE, PVL	Slight enlargement of left inferior lateral ventricle	fMRI, MEG
CP05	PVL	PVL	fMRI, MEG
CP06	N/A	No visible lesion	fMRI, MEG
CP07	HIE, ICH, PVL	PVL, lesion in right thalamus	fMRI
CP08	N/A	No visible lesion	fMRI, MEG
CP09	PVL	Enlargement of lateral ventricles	fMRI
CP10	N/A	Slight enlargement of right lateral ventricle	MEG
CP11	N/A	Small lesion in right anterior frontal lobe	fMRI, MEG

fMRI = functional magnetic resonance imaging, MEG = magnetoencephalography, PVL = periventricular leukomalacia, HIE = hypoxic-ischemic event, ICH = intracranial haemorrhage, IVH = intraventricular haemorrhage, N/A = information not available.

the lesion information of the CP patients. The exact classification of the lesion was not available for all patients. Of the 27 control group members, 19 participated in the sensorimotor tests.

2.2. Experimental setup

2.2.1. Resting state recordings in fMRI and MEG

The MRI imaging was carried out using a 3T-Magnetom Skyra whole-body scanner (Siemens Healthcare, Erlangen, Germany). We used a 32-channel head coil for both structural and functional imaging. All MRI measurements were carried out in the Advanced Magnetic Imaging Centre (AMI) of Aalto University, Espoo, Finland.

Functional MRI data was obtained using a standard echo-planar imaging (EPI) spin-echo sequence with repetition time (TR) of 2.5 s and echo time (TE) of 30 ms. A functional volume consisted of 44 slices with a slice thickness of 3 mm and field of view (FOV) of 192x192 mm^2. This yielded a voxel size of 3x3x3 mm^3. The flip angle was 90°. The resting state measurement was done in one 10-minute-long session, except for one subject who had the session divided into two 5-minute sessions due to the discomfort of being in the scanner for a long time. The subjects were instructed to relax, not to think about anything in particular and to focus their gaze at a fixation cross on gray background.

MEG recordings were conducted at the MEG Core, Aalto NeuroImaging, Aalto University, using a whole-scalp 306-channel (204 gradiometers, 102 magnetometers) MEG system (Vectorview™, Elekta Oy) inside a three-layer magnetically shielded room (Imedco AG) to reduce external interferences. The head position was continuously monitored using five head position indicator coils attached to the head (Fastrak, Polhemus). Prior to the MEG measurement, the position of fiducial points, head position coils, and approximately 200 scalp surface points were registered. The electrooculogram signal was recorded using a pair of electrodes placed below and above the left eye.

MEG measurement was divided into two 5-min sessions with a small pause in between. Participants were asked to sit in a relaxed position, not to think about anything in particular, and to focus their gaze on a fixation cross presented in front of them on a translucent screen. The participants were offered a chance to exit the device and move between the two measurements, but none did.

2.2.2. Anatomical MRI

During the MRI session, high-resolution structural T1-weighted (MP-RAGE) MRI volumes were scanned for each participant. We used 176 slices with a slice thickness of 1 mm and FOV of 256x256 mm, yielding a voxel size of 1x1x1 mm. TR and TE were 2.53 s and 3.3 ms respectively. The flip angle was 7°. The same structural image was used for MEG source reconstruction.

2.2.3. Behavioural sensorimotor skill tests

The participants completed the box-and-block test (Mathiowetz et al., 1985a, 1985b) and the nine-hole peg test (Mathiowetz et al., 1985c) to quantify their gross and fine dexterity of the hands, respectively. In addition, they did a hand kinesthesia test measuring the ability to move the hand accurately to a predefined target on a table (Sensory Integration and Praxis Test, WPS, Torrance, California, US). These tests were conducted in a separate session that was not on the same day as the neuroimaging measurements. In the box-and-block test, the participants moved unilaterally blocks from one box to another as fast as possible. The number of blocks moved in one minute was measured. In the nine-hole peg test, the participants unilaterally picked up small pegs from a plate and placed them in the holes on a board one by one, and then moved them back to the plate one by one as fast as possible. The time to finish the task was measured. The kinesthesia test measured the accuracy (in mm) of hand movement to a predetermined target without visual guidance. The test was repeated ten times with different targets. In all tests, the right and left hand was tested separately but were pooled together as a mean result. Scores were normalized to zero mean and unity variance for statistical testing and the approximate normality of the score distributions was ascertained using a normal-probability plot (Chambers et al., 2018).

2.3. Cortical regions of interest

We chose target regions of interest (ROIs) from the Harvard-Oxford probabilistic atlas, originally distributed with FSL software (Jenkinson et al., 2012). This parcellation has been widely used enabling easier comparisons to precious studies. Furthermore, while finer parcellations of the sensorimotor network exist, MEG would have issues separating the smaller regions. We limited our study to the cortical regions due to MEG having problems distinguishing deeper sources. Further, to limit the scope of the study to the hypotheses about sensorimotor network we picked cortical ROIs that are associated with sensorimotor processing. Table 3 presents the selected ROIs, and Fig. 1 shows their location in the Mon-

Table 1
Subject demographics in fMRI and MEG recordings.

Measurement	Group	Participants	Age	Handedness
MEG	TD group	10 M, 14F	14.1 ± 2.6	22 R, 2 L
	CP group	6 M, 3F	13.4 ± 2.2	5 R, 4 L
fMRI	TD group	10 M, 17F	14.2 ± 2.5	26 R, 1 L
	CP group	5 M, 4F	13.2 ± 2.1	5 R, 4 L

fMRI = functional magnetic resonance imaging, MEG = magnetoencephalography, TD = typically developed, CP = cerebral palsy, M = male, F = female, L = left, R = right.

Table 3
Regions of interest (ROIs) arranged to clusters. Each ROI is split across the hemispheres.

Cluster	ROIs
Sensorimotor	Precentral Gyrus (PreCG)
	Postcentral Gyrus (PostCG)
	Supplementary Motor Area (SMA)
	Parietal Opercular Cortex (POC)
	Central Opercular Cortex (COC)
Frontal	Superior Frontal Gyrus (SFG)
	Middle Frontal Gyrus (MFG)
	Frontal Pole (FP)
Posterior parietal	Superior Parietal Lobule (SPL)
	Anterior Supramarginal Gyrus (SMGa)
	Posterior Supramarginal Gyrus (SMGp)
	Angular Gyrus (AG)

treal Neurological Institute (MNI) average brain (Mazziotta et al., 2001a, 2001b, 1995). These ROIs include primary and secondary somatosensory and motor areas, somatosensory associative areas and areas related to somatosensory salience. They were arranged into clusters with one cluster representing the typical sensorimotor network regions (Biswal et al., 1995; Damoiseaux et al., 2006; Smitha et al., 2017) and the rest arranged according to their anatomical location into either frontal or posterior parietal clusters. Typically, in functional network connectivity studies, some posterior parietal and frontal regions would be clustered together to form default mode, attention or salience networks. However, this approach should be less suitable for MEG where nearby regions are not always independent due to spatial leakage and separating multiple interlaced networks is difficult even if pairwise signal leakage can be corrected for.

2.4. Data processing

2.4.1. FMRI preprocessing

The fMRI data was preprocessed using the Conn toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012) for MATLAB (“MATLAB,” 2020, version R2020b), which utilizes SPM12 tools for MATLAB. We used a standard “SPM pipeline” for ROI-to-ROI analysis in Conn toolbox, with the following steps in order: realigning functional scans to the first scan using b-spline interpolation (Andersson et al., 2001), correcting for slice-timing misalignment which arises from long acquisition time (Henson et al., 1999), identification of outlier scans in terms of movement and bold signal change (outlier thresholds of 0.5 mm and 3 standard deviations respectively), segmentation of gray matter, white matter and cerebrospinal fluid for both functional and structural data, and resampling the data to MNI-space using 4th order spline interpolation (Ashburner and Friston, 2005).

The fMRI data was denoised using a regression model suppressing several noise-related components. Regressors included five (Behzadi et al., 2007; Chai et al., 2012; Muschelli et al., 2014) principal components of the BOLD signals measured from white matter and cerebrospinal fluid respectively (aCompCor), subject motion parameters including three-dimensional translation and rotation, and associated first derivatives (12 parameters in total) and scrubbing components corresponding to outlier scans detected during preprocessing. Finally, the data was band-pass filtered between 0.008 Hz and 0.09 Hz to focus on slow BOLD signal changes.

We computed one time course for each selected ROI. The time course was defined as the first principal component of the time courses of weighted ROI voxel signals, using probabilistic atlas values as weights. Functional connectivity was computed as a Fischer-transformed Pearson correlation of the ROI time courses.

2.4.2. MEG preprocessing

We applied oversampled temporal projection (Larson and Taulu, 2017) to reduce uncorrelated sensor noise in the measurements. This method reconstructs each sensor data, in turn, using the other sensors, thus removing the sensor noise-related component that is uncorrelated with other sensors. External interferences in the measurement were reduced with temporally extended signal space separation (Elekta Maxfilter; Taulu and Simola, 2006). The same software was used to correct for head movement and equalize the head position between our two 5-minute measurements. We then applied independent component analysis (ICA) in conjunction with the EOG electrode measurement to remove eye related artifacts from the data. ICA mixing matrices for artefact removal were estimated from band limited signal between 0.5–45 Hz. We also removed independent components corresponding to cardiac activity after visual inspection. Typically, 3–4 components were removed per participant. Data was 50-Hz notch filtered to remove power line interference, low-pass filtered at 80 Hz, and down-sampled to 200 Hz. Data segments with extensive artefacts due to, e.g., muscular activity, were manually excluded from the analysis.

We measured FC in MEG using band-limited amplitude envelope correlation. This has been found to be a consistent and reliable method for the imaging of brain networks, at least when spatial leakage is corrected for (Colclough et al., 2016). For this purpose, the data was band-pass filtered in four frequency bands: alpha (7–14 Hz), lower beta (14–19 Hz), higher beta (19–30 Hz), and

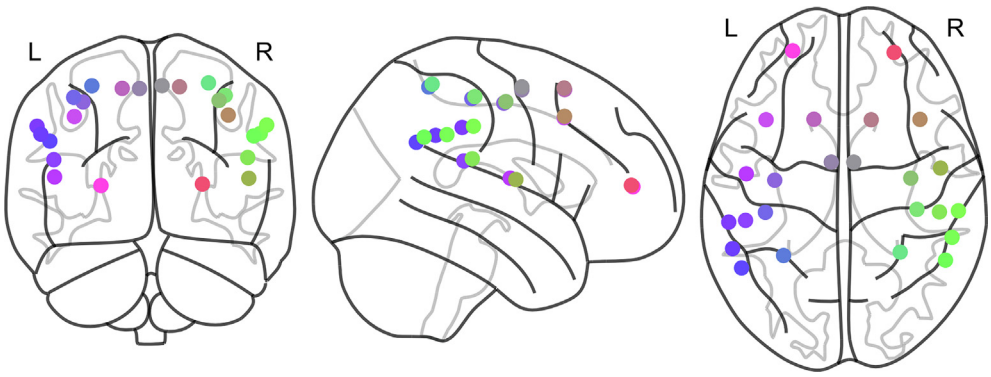

Fig. 1. Region of interest (ROI) center positions in Montreal Neurological Institute (MNI) average brain. Note that in functional magnetic resonance imaging we used the first principal component of the signal in the entire anatomical ROI from Harvard-Oxford atlas and in magnetoencephalography the exact position was individually determined inside the anatomical ROI for each participant. Therefore, these locations should be taken as approximate. The color indicates location, with nearby nodes having similar color, and matches the colors in Fig. 2.

gamma (30–60 Hz). These bands include the most relevant rhythmic activity associated with sensorimotor functions (Cheyne, 2013). Finally, we applied the Hilbert transform to obtain the complex analytic signal.

2.4.3. MEG source estimation

The Freesurfer software v. 6.0 (Dale et al., 1999; Fischl et al., 1999) was applied to segment the brain and skull surface of each participant using the structural MRI scans. The MNE software (Gramfort et al., 2014) was then used to create equally distributed volumetric source space with 5-mm grid density. This resulted in approximately 10,000–15,000 source points for each subject. MNE software was also used to create MEG forward solutions for the source spaces. We used one layer BEM models for the forward computation.

To estimate the source activity, we applied the dynamic statistical parametric mapping (dSPM; Dale et al., 1999) implemented in MNE-python software package (Gramfort et al., 2013). The dSPM method is a noise-normalized minimum norm estimate (Hämäläinen and Ilmoniemi, 1994) where the estimated amplitudes are normalized with the expected source variance under null hypothesis of no activity. This normalization counteracts the superficial source bias inherent to MNE resulting in better location accuracy. This was important to localize the correct maximum-power source within each ROI, but otherwise noise normalization affects neither spatial leakage nor point-source correlation estimates. We used both gradiometers and magnetometers. For computational simplicity, we projected the inverse operator to the direction of the highest source power according to the measured data covariance (Brookes et al., 2011a; Wens et al., 2014).

The Harvard-Oxford atlas defined in MNI standard brain space was morphed to each participant-specific source space using volumetric source space morphing tools in MNE-python (Avants et al., 2008). In each anatomical ROI, we chose the maximum source power point as the representative source for the given region. The maximum point was chosen separately for each frequency range of interest.

We employed a geometric correction scheme (GCS) for spatial leakage (Della Penna et al., 2019; Wens et al., 2015). This method computes the point-spread leakage from a selected seed source location and subtracts it from the other sources to remove the effect of the seed from the target source estimates. We defined each of the selected ROIs in turn as the seed, whose signal was reconstructed from the uncorrected dSPM inverse operator. Other ROI signals (targets) were reconstructed using the inverse operator GCS corrected for the chosen seed. Preference of GCS over the more conventional pairwise or symmetric signal orthogonalization schemes (Brookes et al., 2012; Colclough et al., 2015) was motivated by not losing actual zero-lag interactions. For each node, we computed the amplitude envelope as the absolute value of the analytical signal obtained via Hilbert transform. Connectivity was computed as the Fischer-transformed Pearson correlation of these amplitude signals. The upper and lower triangles of the resulting ROI-to-ROI connectivity matrix were then averaged because leakage correction induces asymmetries (i.e., the correlation from seed A to target B is not exactly the same as from seed B to target A). Such asymmetries are indicative of leakage-correction errors (Colclough et al., 2015), although in this case, they are relatively small since MNE spatial leakage is intrinsically symmetrical (Hauk and Stenroos, 2014).

2.5. Statistical analysis

We assessed functional connectivity differences in the previously defined ROI-clusters between patient and control groups using a cluster level multivariate parametric general linear model (GLM). The model uses a likelihood ratio test using Wilks' lambda statistic which is approximated using F-distribution, producing F-scores and associated cluster level p-values. With nuisance covariates, this corresponds to the multivariate analysis of covariance (MANCOVA). Cluster level comparisons still included up to 25 individual ROI-to-ROI FC values as dependent variables, so we reduced the dimensionality of the data in each test using Principal component analysis (PCA). A maximum of three most prominent features were tested. The number of components was determined so that we had at least 10 data points per tested feature. Due to differences in average handedness of our groups, we included handedness as a nuisance variable in the model.

In addition to testing for group differences, we tested the effect of motor performance scores on the functional connectivity values. We used multiple regression test implemented using GLM. This tests for the effect of the sensorimotor performance scores on the FC within or between the ROI clusters while controlling for the handedness nuisance variable. Due to group differences in motor scores, which would have caused multicollinearity problems, and the small size of the CP group, we only tested the motor variables for the control group.

We applied false discovery rate (FDR) correction for multiple comparisons (Benjamini and Hochberg, 1995) in cluster level tests with a corrected significance threshold of $p < 0.05$ for fMRI and $p < 0.05/N_{band}$ for MEG, where N_{band} is the number of frequency bands tested. For each significant cluster level connection, we applied post-hoc bivariate analysis of the ROI-to-ROI differences, using two tailed t-statistic, and report the individual connections with significant effect with an uncorrected threshold of $p < 0.05$.

3. Results

Functional connectivity. The individuals with CP showed stronger FC than healthy controls. This was visible in both the significant FC changes and in the global average FC change over the ROIs. Several significant FC differences were detected between CP and their healthy peers in both fMRI and MEG. However, MEG and fMRI methods yielded different connectivity difference results. Table 4 lists significant cluster level tests both for fMRI and MEG.

In fMRI, the children with CP showed enhanced within cluster connectivity in the parietal cluster of each hemisphere than healthy controls. In addition, there was a trend of increased connectivity in the other clusters, which can be seen in Fig. 2B. However, the differences in other clusters were not significant.

Table 4
Significant cluster level statistical results (CP > control). P-values are FDR corrected. Differences in degrees of freedom (DoF) result from different number of control subjects in MEG and fMRI.

Measurement	Cluster	F-score	DoF	p-value (FDR)
fMRI	Left parietal (within cluster)	7.02	3, 31	< 0.05
	Right parietal (within cluster)	5.34	3, 31	< 0.05
MEG - Alpha	Left parietal – Right sensorimotor	9.75	3, 28	< 0.01
MEG - Low Beta	Left sensorimotor – Right sensorimotor	8.83	3, 28	< 0.01
	Left parietal – Right sensorimotor	8.20	3, 28	< 0.05

fMRI = functional magnetic resonance imaging, MEG = magnetoencephalography.

In MEG, the patients with CP showed higher interhemispheric connectivity than healthy controls. In alpha band, only the connectivity between left posterior parietal and right sensorimotor clusters showed a significant increase between them. No significant differences were observed between the groups in higher beta band or gamma band. In lower beta band, interhemispheric synchronization was stronger between primary sensorimotor cortices, as well as between right primary sensorimotor cortex and left posterior parietal areas, especially supramarginal gyrus. The MEG post-hoc differences are presented in Fig. 2C–F.

Group average FC z-scores across the test subjects were very highly correlated between the MEG bands (Pearson's $\mathbf{r} > 0.9$) and weakly but significantly correlated between the MEG bands and fMRI (Pearson's $\mathbf{r} > 0.22$, $p < 0.0001$, for all bands). The group difference effect, however, was not significantly correlated between fMRI and MEG.

Sensorimotor performance. As expected, the individuals with CP showed worse fine-motor skill (9-hole-peg test duration, CP: 21.24 ± 1.72 s vs. controls: 18.08 ± 1.99 s, $p < 0.05$) and gross-motor skill (box-and-block test number of blocks, CP: 56.43 ± 11.03 vs. controls: 70.18 ± 6.63, $p < 0.005$) than healthy controls. Mean kinesthesia accuracy was slightly worse for the CP group but not statistically significantly (CP: 2.77 ± 0.44 cm vs. controls: 2.38 ± 0.71 cm, $p \approx 0.13$).

In the healthy controls, the motor skill scores of the hands did not have a statistically significant connection to the FC values in our testing framework. Please note that the associations between FC values and sensorimotor performance were not assessed in the CP population due to a small sample size ($N = 9$). The kinesthesia test score showed statistically significant relationship between right side posterior parietal and frontal regions on MEG lower beta frequency range ($F(3,14) = 14.49$, $p(\text{FDR}) < 0.01$). Other frequency ranges did not reveal statistically significant results. FMRI did not show significant results. The post-hoc results are presented in Fig. 3, which illustrates an overall trend of positive correlation between motor performance and functional connectivity in the control group. This contrasts with the group level comparisons, CP group having higher connectivity values but lower motor performance.

4. Discussion

We observed stronger resting state functional connectivity associated with spastic diplegic CP across sensorimotor regions when compared to their healthy controls. The enhanced connectivity was spatially markedly different between the used neuroimaging modalities (MEG vs. fMRI). In MEG, the interhemispheric connections were strengthened in CP, as well as connectivity of the parietal regions, whereas fMRI revealed enhanced intrahemispheric within cluster connectivity of the parietal regions in CP. The resting state connectivity was associated with better kinesthesia performance in the healthy control population.

4.1. Resting state functional connectivity in diplegic CP

It is not clear which neurophysiological mechanism causes the enhanced connectivity in CP. While correlated activity indicates anatomic connections between regions the path is not necessarily direct. Furthermore, increased correlation can happen both due to stronger correlated inputs and due to weaker uncorrelated inputs. A hypothesis for the cause could therefore be either that the weaker afferent inputs reduce specific inputs to the different ROIs, resulting in relative strengthening of cortico-cortical connections, or that the disruption of the inputs has altered the development of the network making the alternative cortico-cortical connections stronger.

There is previous evidence of reduced spatial specificity and increased correlation of activity in somatosensory regions in spastic CP when compared to healthy controls in resting-state fMRI (Burton et al., 2009). It has been hypothesized that periventricular white matter injuries in diplegic CP may diminish the afferent thalamocortical somatosensory inputs, which may abnormally strengthen the competing intracortical interactions. Same reasoning has been suggested for overall increase in connectivity of cortical sensorimotor network (Mu et al., 2018). In addition, impairment of thalamocortical and cortico-basal ganglia-thalamocortical loop, that has been suggested to influence sensory processing of movements (Humphries and Gurney, 2002), could explain increased intracortical interaction also by reduced cortical inhibitory functions (Vry et al., 2008). Reduced inhibition in the somatosensory cortex may explain why children with CP tend to show stronger fMRI activation in peripheral somatosensory stimulation (Nurmi et al., 2021). A possible explanation for both increased connectivity and stronger BOLD response for stimulation could be a lack of coherent stimulation of the relevant cortical regions in early development. This could lead to abnormally developing networks, the existing intracortical connections dominating, and lack of specificity in cortical function with respect to peripheral connections. This lack of specificity could be one explanation of the motor symptoms in CP. However, the effects of CP in our results are small even when statistically significant, suggesting that the sensorimotor network itself is not fundamentally altered by the white matter lesions in our test population. This further suggests that brain plasticity can for the most part preserve the functional network structure in perinatal white matter injury. In our study we limited the participation to subjects with normal cognitive abilities and sufficient motor ability. While we find these kinds of limitations necessary for practical group comparisons, this also disqualifies some larger lesions that could offer more insight into how the lesion size and location affects the FC results.

Some previous studies have reported an association between FC and motor performance (Linke et al., 2018; Simon-Martinez et al., 2019; Wheelock et al., 2018) but others have not (Saunders et al., 2019). It has also been suggested that periventricular white matter damage would impair visuomotor development (Bauer and Papadelis, 2019) which would affect hand coordination performance. However, it is not clear if changes to cortical FC should directly reflect this. Recently it has been reported that kinesthetic ability is linked to functional connectivity between various cortical regions but the direction of the correlation differs according to subject age (Yoshimura et al., 2020). In the suggested mechanism, age-related "lower-level" dysfunctionality results in compensatory enhanced activity of "higher-level" somatosensory and motor regions. Another work found that age-related decrease in proprioceptive inputs in bimanual tasks on elderly subjects results in enhanced compensatory neural activity in inferior parietal and dorsolateral prefrontal areas (Goble et al., 2010). Furthermore, elderly subjects have been found to have enhanced FC of SM1 to frontal and inferior parietal areas (Landelle et al., 2020) in line with the "compensation-related utilization of neural circuits hypothesis" (Reuter-Lorenz and Cappell, 2008). While task-related compensatory activity is not necessarily directly related to FC, the phenomenon where affected sensory input results in more intensive processing activity could be similar. For example, cortical processing of cortico-peripheral coupling during proprioceptive stimulation is enhanced in older individuals compared to younger ones, and the enhanced processing predicts worse standing postural balance performance (Piitulainen et al., 2018). Lesions in the young brain could, possibly, cause similar functional effects to aging related dysfunctions.

Our results show that increased resting state FC correlates with better sensorimotor performance in healthy young subjects. The

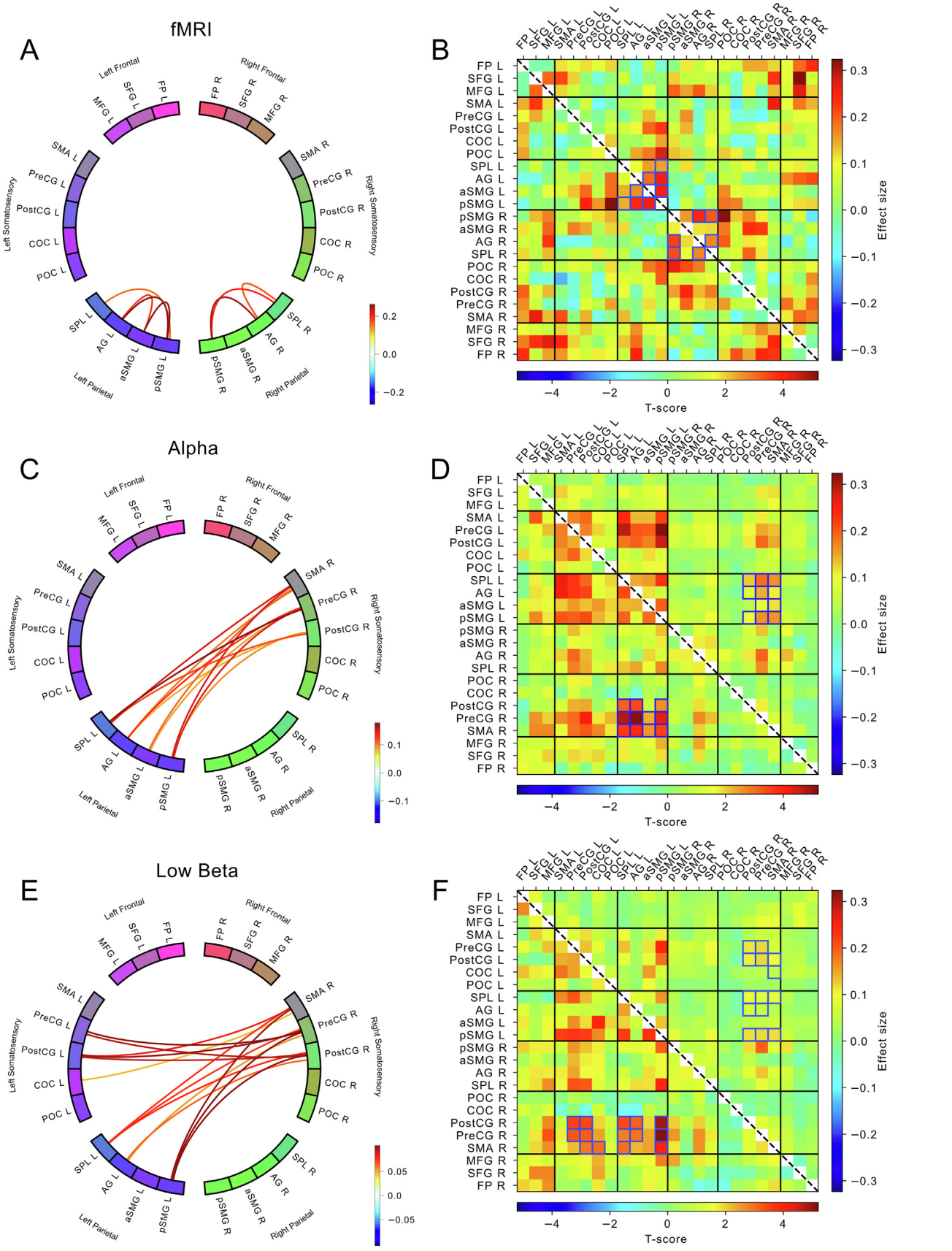

Fig. 2. Group differences (CP > control) in functional cortical connectivity for fMRI and MEG. Left: Connectivity circle with the post-hoc significant connections for (A) fMRI, (C) MEG alpha and (E) lower beta bands. Right: Group difference matrices for (B) fMRI, (D) MEG alpha and (F) lower beta bands with upper and lower halves showing the effect size and the post-hoc T-statistic respectively. The post-hoc significant differences ($p < 0.05$) have been highlighted in blue. Refer to Table 3 for explanation of abbreviations.

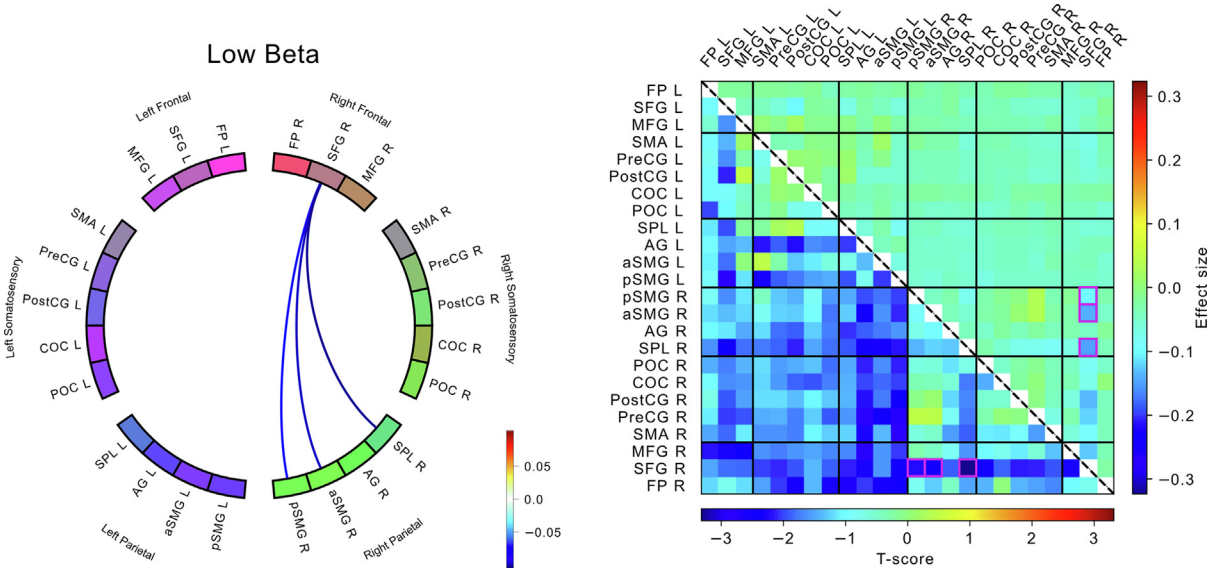

Fig. 3. Kinaesthesia score was statistically related to FC scores between right frontal and right posterior parietal areas. Kinaesthesia score is smaller for better performance so negative values indicate that connectivity is positively correlated with kinaesthesia performance. Refer to Table 3 for explanation of abbreviations.

only significant correlation in the current study was with kinesthesia ability and frontoparietal connection of lower beta frequency amplitude. However, the general trend was the same with several other connections in MEG beta frequencies, with the possible exception in intrahemispheric connections within the sensorimotor cortex. The finding on significance of frontoparietal connectivity is also in line with our previous reports finding similar responses to proprioceptive stimuli in frontal and posterior parietal regions (Vallinoja et al., 2021). However, the found significant correlation was not associated with the same ROIs that were affected in the CP group. Hence the hand coordination performance problems in CP cannot be sufficiently explained by FC differences we found. There are likely multiple mechanisms at work. Lesion induced changes can appear as increased FC as suggested above, but this mechanism does not necessarily relate to the higher-level sensorimotor processes that produce the effect in the healthy population. As a clinical consequence the resting state FC is likely not a reliable predictor of motor ability in CP.

Both MEG and fMRI results indicated increased connectivity of the posterior parietal cortex in diplegic CP. The superior parietal lobule has been widely associated with a variety of sensory processing tasks such as somatosensory and visuomotor integration (Culham and Valyear, 2006; Iacoboni, 2006), motor learning and spatial perception (Weiss et al., 2003). Angular gyrus has been mostly connected to higher-order functions such as recognition and comprehension, with known connections to multiple areas in the cortex (Seghier, 2013). Similarly, a wide array of tasks has been associated with supramarginal gyrus, including word processing (Sliwinska et al., 2012; Stoeckel et al., 2009), spatial awareness and proprioception (Ben-Shabat et al., 2015; Kheradmand et al., 2015). In addition to the previously mentioned impairment of thalamocortical tracks, it is likely that periventricular lesions reduce connectivity to more distant cortical areas and in comparison, enhance local connectivity with nearby parietal regions.

4.2. MEG vs. fMRI resting state functional connectivity

Previous multimodal neuroimaging experiments have shown similarities in the network structures emerging from fMRI and in some frequency bands of MEG signals (Brookes et al., 2011a, 2011b; Tewarie et al., 2014). In the current study, the group average FC values were weakly correlated between MEG and fMRI, although our focus was on group differences in network structures. Group differences in MEG and fMRI in our study were not correlated. This difference between the imaging modalities may arise from the methodological differences of MEG and fMRI that are measuring overlapping but different physiological processes. MEG measures the electrophysiological activity of the neurons and fMRI the hemodynamic activity. The currently applied band limited MEG signals reflect relatively short time scale oscillatory neuronal activities (<1 s) at relatively high frequency bands (>10 Hz), while the fMRI signal reflect overall neuronal activity over longer periods (several seconds). Therefore, fMRI does not necessarily capture similarly the differences in the functional connectivity associated with the high frequency oscillatory processes of the neurons. In the present study fMRI was unable to find the enhanced interhemispheric connectivity that MEG uncovered. It is likely that, as previously stated, with MEG we can capture shorter time frame correlation between brain regions that could average out in longer fMRI signal and which fMRI would be unable to reliably measure. We would therefore argue that multiple imaging modalities should be used more frequently to better understand the functional networks in the brain.

Alpha and beta frequency bands had highly correlated FC characteristics. This is not entirely unexpected, there have been high inter band correlation between alpha and beta MEG envelopes in previous studies (Cabral et al., 2014; Godfrey and Singh, 2021; Tewarie et al., 2016). While there were some differences in statistical significance of group comparisons in alpha and beta frequencies the overall direction of differences is similar between the bands. In other words, spastic cerebral palsy seems to cause parallel changes in both alpha and beta frequencies. This suggests that interpreting brain signals as band limited oscillations could be insufficient approach. When looking at frequency bands separately we implicitly assume that alpha band oscillation is separate process from beta band oscillation and that they form separate networks. Future work should perhaps consider looking for a method that can integrate data from multiple frequency ranges or look at wider band activity.

In addition, there are several other factors and methodology specific limitations that need to be considered when comparing the results and are thus discussed below in more detail.

fMRI-related limitations. Both motion artefacts and common methods to correct for them tend to strengthen local correlations and connections in lateral directions and weaken longer anterio-posterior connections (Power et al., 2014). Our participants with CP moved their head significantly more than their healthy peers during the MRI measurements (mean displacement: CP 0.19 ± 0. 1 mm, TD: 0.11 ± 0.05 mm, $p < 0.05$). Fig. 2 shows the relatively symmetric nature of the detected differences in fMRI connectivity, with local connectivity strengthened bilaterally and slight (albeit statistically non-significant) reductions in frontoparietal connectivity. Although we applied state-of-the-art motion artefact corrections, it is still possible that motion related effects remained. It has proven difficult to adequately remove the motion effects from resting state fMRI without introducing new artefacts related to the correction (Parkes et al., 2018). Therefore, some caution is needed when interpreting the current functional connectivity fMRI results. However, the mean head motion during measurement was not significantly correlated with the functional connectivity in the reported regions, thus our results likely reflect true physiological differences between the studied populations. The correction of motion artefacts can result in some false negatives in our reporting.

MEG-related limitations. By the nature of the measurement, separating nearby sources is challenging due to spatial leakage of the cortical sources to the surrounding areas. The used leakage correction method removes direct spatial leakage in pairwise comparisons, but leakage still affects the inference indirectly. For example, we determined the node locations in each anatomical ROI from the uncorrected dSPM solution, leading to potential biases towards possible stronger sources in other ROIs. Although we eliminated false correlation due to direct point spread by correcting pairwise leakage from the seed, we did not correct for the secondary leakage between the target nodes. These limiting factors may explain why no differences between CP and control groups were detected in the local functional connectivity of the nearby ROIs.

4.3. Conclusion

Our results indicated enhanced FC in between several sensorimotor cortical regions in adolescents suffering from spastic diplegic CP when compared to their healthy peers. The enhanced FC was evident both from MEG and fMRI data, although these methods indicated neuroanatomially different results. The two imaging modalities can measure different processes and distinguish different changes in FC. Just one imaging modality should not be considered authoritative when interpreting large scale brain network models. In addition, sensorimotor task performance was positively correlated with frontoparietal FC of beta amplitude in the healthy controls. There are likely multiple overlapping mechanisms affecting the observed FC differences between CP and control groups and it would be good in the future studies to consider the if the effect of the brain lesion to FC is directly comparable to FC differences in healthy brain when interpreting the FC results between patients and healthy individuals.

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Conflict of Interest

None of the authors declared any conflict of interest.

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