Restoring Functional Connectivity in Hemiplegic Cerebral Palsy: A Study of Low-Frequency rTMS Intervention

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ABSTRACT

Background: Hemiplegic Cerebral Palsy (HCP) causes significant motor impairments, due to disrupted Functional Connectivity (FC) between brain regions. Low-Frequency Repetitive Transcranial Magnetic Stimulation (LF-rTMS) has emerged as a potential therapeutic technique for restoring FC and motor recovery.

Objective: This study aimed to evaluate the effects of LF-rTMS on FC in children with spastic HCP.

Material and Methods: This Randomized Controlled Trial (RCT) included ten children with spastic HCP, aged 4 to 13 years. Six children received 12 sessions of LF-rTMS, while four in the control group underwent 12 sessions of sham stimulation. Functional Magnetic Resonance Imaging (fMRI) was used to assess intra- and interhemispheric FC during passive knee movements of the affected limb.

Results: LF-rTMS induced region-specific reductions in interhemispheric FC, particularly between the contralesional ventral premotor area (cPMv) and both the ipsilesional primary somatosensory cortex (iS1) (for effect size: T=-2.60, *P*-value=0.048, FDR-corrected) and the ipsilesional primary motor area (iM1) (T=-2.45, *P*-value=0.048, FDR-corrected). These findings suggest modulation of interhemispheric motor-sensory pathways. Concurrently, localized increases in FC were observed in contralesional regions, and FC decreased between the ipsilesional Supplementary Motor Area (SMA) and the secondary somatosensory cortex (S2) (T=-3.11, *P*-value=0.041, FDR-corrected).

Conclusion: LF-rTMS may modulate FC and hold promise as a rehabilitative intervention for improving motor function in children with HCP.

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Keywords

Cerebral Palsy; Transcranial Magnetic Stimulation; Functional Connectivity; Magnetic Resonance Imaging

Introduction

Cerebral Palsy (CP) is a neurological disorder, primarily characterized by motor deficits, notably affecting walking abilities [1]. The most prevalent subtype is Hemiplegic Cerebral Palsy (HCP), characterized by unilateral motor dysfunction [2-4]. Children with HCP often exhibit an imbalance in interhemispheric Functional Connectivity (FC), with increased and decreased excitability in the unaffected and the affected hemisphere, respectively [5-9]. FC, which reflects the coordinated activity between brain regions, is essential for motor control [10]. A pronounced interhemispheric inhibitory imbalance in HCP has been linked to poorer motor performance [11].

Low-frequency repetitive transcranial magnetic stimulation (LF-rTMS) has emerged as a viable rehabilitation technique for motor recovery in children with hemiparesis [12-20]. This approach aims to restore interhemispheric balance by reducing overactivity in the unaffected hemisphere and promoting restoration in the damaged hemisphere [21]. By enhancing the activation of affected brain regions, LF-rTMS supports motor recovery [6,22-24]. Functional magnetic resonance imaging (fMRI) is a non-invasive tool for examining brain processes, particularly motor cortex FC, in children with HCP [25]. However, despite the LF-rTMS's potential, its specific effects on intra- and interhemispheric FC during motor tasks remain poorly understood, particularly in pediatric populations with HCP.

While evidence supports the use of LF-rTMS in neurorehabilitation, the specific effects of that on FC during passive movements of the affected knee remain unclear. Previous studies have focused mainly on general motor outcomes, creating a gap in understanding how LF-rTMS impacts intra- and inter-hemispheric FC during task-specific neural reorganization. This study addresses this gap by examining the effects of LF-rTMS on FC during passive knee movements in children with HCP.

Material and Methods

This randomized controlled trial (RCT) compares the effects of LF-rTMS versus sham stimulation on functional connectivity in children with HCP (IRCT2016092525568N2).

Participants

The study involved ten children with spastic HCP (ages 4-13; 5F, 5M), which were randomly assigned to either the treatment group, or the control group. Inclusion criteria required significant lower limb spasticity and the absence of severe mental impairments. Before the experiment began, written informed consent was obtained from the parents or guardians of all participants. The study was approved by the Ethics Committee of the Tehran University of Medical Sciences (TUMS) in Iran.

Repetitive transcranial magnetic stimulation (rTMS) treatment

A specialized coil was used to stimulate the motor area responsible for lower limb control, located deep within the primary motor cortex. The optimal stimulation site was determined using single-pulse TMS, increasing intensity until the motor-evoked potential (MEP) achieved a peak-to-peak amplitude larger than 50 microvolts. The treatment group received low-frequency (1 Hz) rTMS four times weekly for three weeks, while the control group received sham rTMS with the coil positioned vertically [26-28].

Treatment protocol

Figure 1 illustrates the treatment protocol, which underwent LF-rTMS for 12 sessions, administered four times per week over three weeks. The control group received 12 sessions of sham stimulation under identical conditions. Both pre-intervention and three weeks post-intervention were assessed [28-31].

MRI data acquisition

Structural (T1-weighted) and fMRI were obtained using a 3-Tesla GE scanner equipped with a 24-channel RF coil and single-shot echo-planar imaging (SS-EPI).

Structural scans were captured using a Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) pulse sequence (repetition time (TR)=1800 ms, echo time (TE)=3.42 ms, inversion time=450 ms, flip angle (FA)=7°, sagittal slices, 1 mm^3 isotropic voxels, and a matrix size of 192×192 mm^2). Functional images were obtained using an EPI sequence

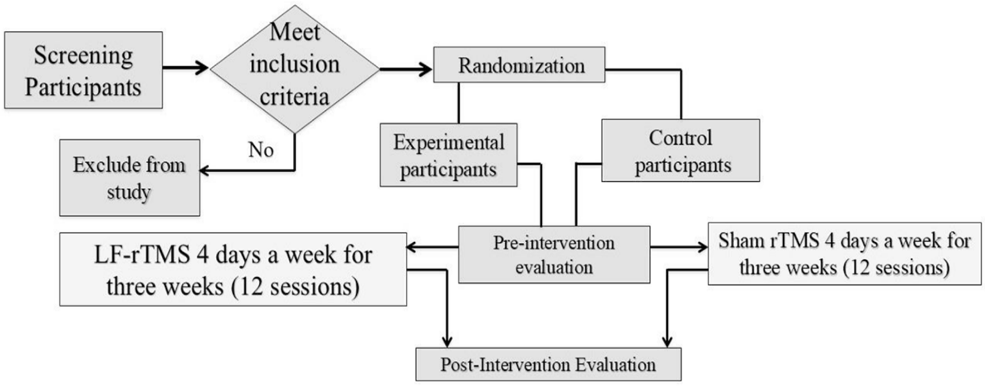

Figure 1: The treatment protocol involved low-frequency repetitive transcranial magnetic stimulation (LF-rTMS) for three weeks, while the control group received sham rTMS for the same duration. Functional Magnetic resonance imaging (fMRI) evaluations were conducted both initially and post-intervention.

with these parameters (TR=3000 ms, TE=30 ms, and FA=90°, an acquisition matrix size of 64×64, and 39 transverse slices with a voxel size of 3.59×3.59×3 mm^3).

MRI scans were performed at both pre-intervention and after three weeks of treatment. During fMRI, a trained biomedical engineer supervised the affected limb's passive knee plantar/dorsiflexion movements, following a block design paradigm of 24 seconds of rest followed by 24 seconds of motor tasks.

fMRI parameters

After image processing, FC parameters (intra- and interhemispheric FC) were calculated. Intra-hemispheric FC examined connections within the same hemisphere, while inter-hemispheric FC assessed connectivity between hemispheres.

Functional Connectivity Magnetic Resonance Imaging (fMRI)

FC during passive movement of the affected knee was evaluated using MATLAB (R2018b) and the CONN toolbox (v22.a), which is based on the SPM (Statistical Parametric Mapping) framework [32-34]. Functional connectivity magnetic resonance imaging (fcMRI) assesses brain network integration by examining temporal correlations in blood oxygenation level-dependent (BOLD) signal fluctuations across predefined regions of interest (ROIs). This study's ROIs comprised the corpus callosum (CC), premotor cortices (dorsal PMd and ventral PMv), motor (M1) cortex, primary (S1) and secondary (S2) somatosensory cortices, and supplementary motor area (SMA) in the ipsilesional and contralesional hemisphere.

This toolbox provides a full set of fcMRI analysis tools, including spatial preprocessing, BOLD time series denoising, first-level connectivity analysis, and second-level connectivity analysis.

Spatial Preprocessing

The preprocessing pipeline followed standard volume-based protocols, which included realignment and unwarping to remove motion and susceptibility artifacts, as well as slice-timing correction to align temporal BOLD acquisitions. Outlier detection identifies frames with excessive motion or global signal changes. Segmentation and normalization to the standard MNI space were performed, followed by smoothing with an 8 mm Gaussian kernel to improve signal-to-noise ratio.

Denoising

Denoising eliminated confounding signals from white matter, cerebrospinal fluid (CSF), and motion by employing the anatomical component-based noise correction (aCompCor) method. The frequencies of neural signals above 0.008 Hz were retained by applying a temporal band-pass filter.

Functional Connectivity Analysis

First-level Connectivity Analysis

At the first level, ROI-to-ROI connectivity during the task was estimated using weighted least squares (WLS) technique, employed to capture both intra-hemispheric and inter-hemispheric connections.

Second-level Connectivity Analysis

The second level analysis employed a General Linear Model (GLM) to assess differences in FC between the treatment and control groups following the intervention. The GLM design matrix included two groups (treatment and control) and two conditions (before and after intervention).

Group participation was encoded as binary variables (1 for inclusion, 0 for exclusion), and the model accounted for each subject's pre- and post-intervention conditions. A contrast vector of [1 -1] was used to investigate group-level differences after the intervention, with the treatment group, showing greater post-intervention connectivity changes than the control group. In the GLM framework, a voxel-wise t-test was commonly used to determine statistical significance. In the context of neuroimaging, the T-value is commonly interpreted as a two-sample test statistic. A higher absolute T-value indicates a more significant difference in FC between the two groups. The uncorrected *P*-value represents the likelihood of observing the test statistic under the null hypothesis. To account for multiple comparisons, the False Discovery Rate (FDR) correction was used, with p-FDR values less than 0.05 considered statistically significant.

Results

Ten participants were enrolled in the study, with six assigned to the treatment group (60%) and four to the control group (40%). One participant did not complete the experiment. The demographic characteristics of the participants are summarized in Table 1.

First-level connectivity analysis

Figure 2 presents heatmaps of the FC during passive affected knee movements for one participant from the control group and one from the treatment group. The heatmaps indicate the range of FC values, with red and blue hues representing increased positive and negative connectivity, respectively. Notably, post-intervention, FC values in the treatment group were significantly higher than those in the control group.

Second-level Connectivity Analysis

The second-level connectivity analysis identified specific reductions in FC in the treatment group compared to the control group following LF-rTMS. Two-sample t-tests were used for each pair of brain regions to assess these changes. The resulting T-values and uncorrected *P*-values were adjusted using the FDR method, as shown in Table 2. The blue squares in Figure 3 represent statistically significant decreases in FC between treatment and control groups in specific brain regions, as determined by the second-level analysis.

Table 1: Patient demographics

Group	Participants (n=6)	Age (mean±SD)	Gender (Male/Female)
Treatment group	6 (60%)	9.2±2.93	3M/3F
Control group	4 (40%)	7.83±2.31	2M/2F

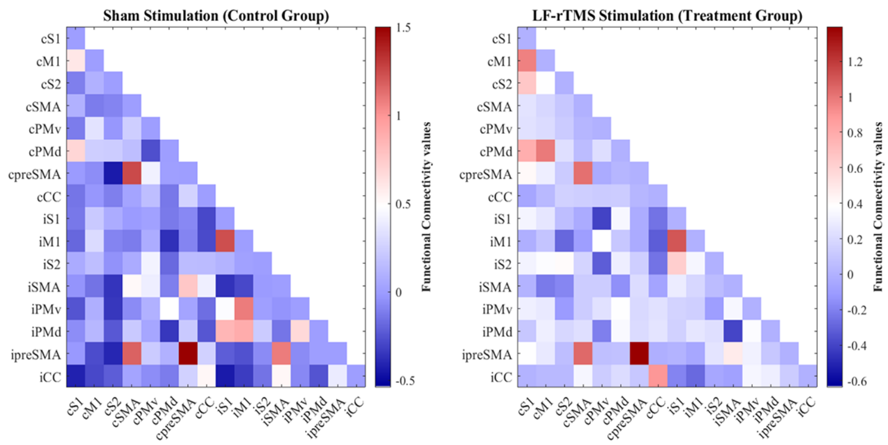

Figure 2: Heatmaps representing functional connectivity (FC) in one participant from the control group (left) and one from the treatment group (right) during affected knee movement. Red hues indicate increased positive connectivity, while blue hues represent negative connectivity. Contralesional regions of interest (ROIs) include the primary somatosensory cortex (cS1), primary motor cortex (cM1), secondary somatosensory cortex (cS2), supplementary motor area (cSMA), ventral premotor cortex (cPMv), dorsal premotor cortex (cPMd), presupplementary motor area (cpreSMA), and cingulate cortex (cCC). Ipsilesional ROIs include iS1, iM1, iS2, iSMA, iPMv, iPMd, ipreSMA, and iCC.

Table 2: Differences in brain functional connectivity (FC) between treatment and control groups after low-frequency repetitive transcranial magnetic stimulation (LF-rTMS) during affected knee movement.

ROI-to-ROI	T-value	p-uncorrected	p-FDR
cPMv-iS1	-2.60	0.025	0.048
cPMv-iM1	-2.45	0.048	0.048
iSMA-iS2	-3.11	0.041	0.048

ROIs: Regions of Interest, FDR: False Discovery Rate, cPMv: contralesional Ventral Premotor Cortex, iS1: ipsilesional primary somatosensory cortex, iM1: ipsilesional primary motor cortex, iSMA: ipsilesional supplementary motor area, iS2: ipsilesional secondary somatosensory cortex

Significant reductions in FC were found between the contralesional premotor ventral cortex (cPMv) and the ipsilesional primary somatosensory cortex (iS1) (T=-2.60, p-FDR=0.048), as well as between the cPMv and the ipsilesional primary motor cortex (iM1) (T=-2.45, p-FDR=0.048). The ipsilesional supplementary motor area (iSMA) and ipsilesional secondary somatosensory cortex (iS2) showed the greatest decrease in FC (T=-3.11, p-FDR=0.048). These findings suggest that LF-rTMS has a specific effect on motor-sensory pathways, as evidenced by statistically significant changes in connectivity confirmed by FDR correction. Figure 3 depicts a summary of these connections, with Table 2 providing additional information.

Percentage of Relative FC Changes between Treatment and Control Groups Post-intervention

Figure 4 displays heatmaps with the

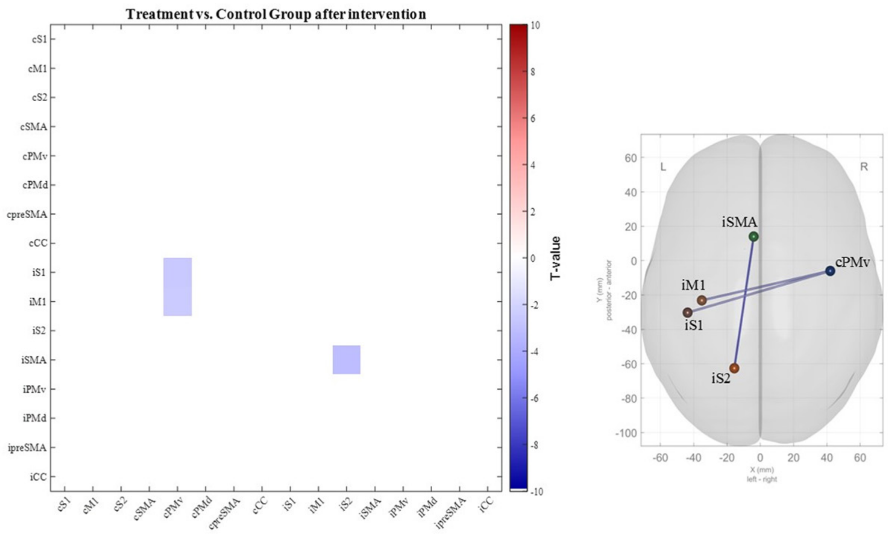

Figure 3: Region-specific reductions in brain functional connectivity (FC) between treatment and control groups after low-frequency repetitive transcranial magnetic stimulation (LF-rTMS). The blue squares represent statistically significant reductions in functional connectivity (FC) between specific brain regions, as identified by the second-level analysis. Reductions were observed between the contralesional premotor ventral cortex (cPMv) and the ipsilesional primary somatosensory (iS1) and motor (iM1) cortices, and between the ipsilesional supplementary motor area (iSMA) and secondary somatosensory cortex (iS2).

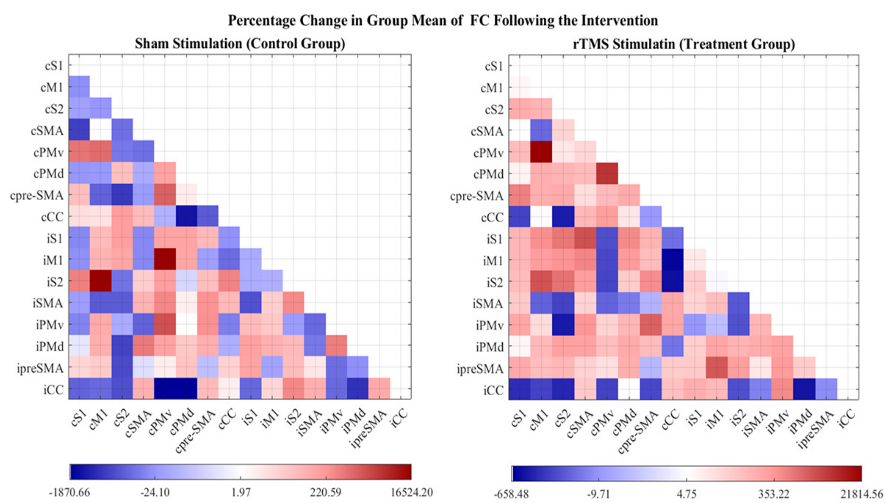

Figure 4: Heatmaps illustrate group mean functional connectivity (FC) changes in the control group (left) and the treatment group (right). Red hues indicate increased positive connectivity, while blue hues represent negative connectivity. Contralesional regions of interest (ROIs) include the primary somatosensory cortex (cS1), primary motor cortex (cM1), secondary somatosensory cortex (cS2), supplementary motor area (cSMA), ventral premotor cortex (cPMv), dorsal premotor cortex (cPMd), presupplementary motor area (cpreSMA), and cingulate cortex (cCC). Ipsilesional ROIs include iS1, iM1, iS2, iSMA, iPMv, iPMd, ipreSMA, and iCC.

percentage change in the group mean of FC changes for the treatment and control groups, comparing post-intervention results to pre-intervention. After the intervention, the treatment group exhibited more substantial increases in FC, particularly in intra-hemispheric FC within both the contralesional and ipsilesional hemispheres. These changes were accompanied by greater variability and a broader range of FC values in the treatment group compared to the control group.

Comparative Analysis of Relative Functional Connectivity (FC) Changes in Treatment and Control Groups Post-Intervention

Following the intervention, the treatment group demonstrated a significant relative increase in FC in the contralesional hemisphere, with a mean change of 1032.23%, compared to a relative decrease of -43.47% in the control group. The standard deviation (SD) in the treatment group (1580.98%) was also much larger than that of the control group (200.86%), indicating greater variability in the treatment group. Similarly, the range of FC values was wider in the treatment group (3906.32%) compared to the control group (699.72%).

In the ipsilesional hemisphere, intra-hemispheric FC also showed significant differences. The treatment group had a mean FC of 136.30%, higher than the control group's 29.81%. Additionally, the treatment group displayed a higher SD (138.98%) compared to the control group (34.18%), as well as a wider range of FC values (338.39% versus 114.24%).

For inter-hemispheric FC, the control group exhibited a higher mean FC (517.95%) than the treatment group (181.80%). However, the control group also showed greater variability, with an SD of 947.89%, compared to the treatment group's SD of 207.51%. The control group also had a larger range of FC values (2605.36%) than the treatment group (694.22%).

Discussion

This study investigated the effects of LF-rTMS on FC during passive movement of the affected knee in children with HCP.

According to the finding, LF-rTMS has distinct effects on intra- and inter-hemisphere connectivity. Following the LF-rTMS intervention, the treatment group's intra-hemisphere FC in the contralesional hemisphere was substantially higher than that of the control group. LF-rTMS may enhance neuroplasticity and support the brain's adaptive reconfiguration during recovery by fostering neural connections in the unaffected hemisphere [35].

The control group, which did not receive stimulation, showed little to no improvement in FC and even a decrease in some areas, highlighting the significance of targeted interventions in promoting neural recovery [36].

Significant interhemispheric FC differences were found between the control and treatment groups, consistent with previous research showing that active rTMS reduces interhemispheric FC while sham increases it [37].

Based on the results, the control group exhibited higher interhemispheric FC changes with considerable variability and a broad range, most likely reflecting unregulated interhemispheric interactions under sham conditions. These findings support the hypothesis that sham interventions may improve overall FC but lack the specificity to disrupt maladaptive transcallosal inhibition [38].

The treatment group had lower mean interhemispheric FC changes, with less variability and a narrower range, indicating stabilized and intentionally modulated connectivity. Active interventions, such as rTMS, appear to enhance interhemispheric interactions by reducing maladaptive transcallosal inhibition, selectively facilitating the nondominant hemisphere, and improving functional outcomes. These findings highlight the therapeutic value of rTMS in regulating connectivity patterns and suggest strategies for improving interhemispheric modulation in clinical and research settings.

Our findings indicate that LF-rTMS has different effects on FC between and within the hemispheres. It strengthens intra-hemispheric connections, especially those in the contralesional hemisphere while modulating inter-hemispheric connections to reduce overactivity and restore balance. This dual effect makes LF-rTMS a promising treatment for HCP and other neurological disorders. Nonetheless, more research is needed to understand the underlying mechanisms of LF-rTMS better and assess its long-term effects.

A key finding of the current study was that LF-rTMS significantly modulated FC between the contralesional ventral pre-motor area (cPMv) and ipsilesional motor and sensory regions. The treatment group showed more substantial alterations in these connections than the control group. These adaptive changes are critical for motor recovery as they facilitate the integration of sensory feedback with motor planning, a process essential for coordinated movement. This observation aligns with previous research highlighting the importance of pre-motor cortex reorganization in motor recovery following brain injury [39].

The reorganization of somatosensory and motor systems is crucial for individuals with motor impairments, such as cerebral palsy or stroke [40,41]. By targeting FC between the pre-motor cortex and sensory regions, LF-rTMS may activate compensatory mechanisms that enhance motor control and recovery [42,43]. This finding supports that effective rehabilitation interventions should address sensory and motor systems to maximize improvements in motor function [44].

The considerable variability observed in groups underscores the need for further research to understand individual factors, such as baseline neurophysiological characteristics or the extent of brain injury, which may contribute to differential responses to LF-rTMS.

Future studies should employ larger sample sizes to enhance the generalizability of findings. Additionally, investigations are needed to elucidate the specific brain mechanisms underlying these alterations and evaluate the long-term effects of LF-rTMS in neurorehabilitation. Furthermore, more extensive research is required to optimize stimulation parameters, refine rehabilitation protocols, and explore the potential of machine learning in predicting individual recovery outcomes and tailoring treatment strategies [45-47].

Conclusion

This study shows that LF-rTMS modifies functional connectivity in children with HCP, specifically between the contralesional pre-motor cortex and the ipsilesional motor and sensory regions. The treatment group demonstrated greater improvements in intra-hemispheric connectivity in the contralesional hemisphere and a more dynamic neurophysiological response. These findings suggest that LF-rTMS may facilitate neuroplasticity and promote brain reorganization.

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Authors' Contribution

A. Ghalyanchi-Langeroudi is primarily responsible for data acquisition, analysis, and drafting of the complete manuscript. E. Yargholi contributed to manuscript preparation through editing and revisions. M. Soleimani played a critical role in interpreting and discussing the study's results. A. Shahrokhi assisted in identifying and recruiting suitable patients for the study. MM. Mirbagheri supervised and managed the entire study, and contributed to manuscript editing. All the authors read, modified, and approved the final version of the manuscrip.

Ethical Approval

The Ethics Committee of Tehran University of Medical Sciences approved the study protocol (Ethic code: IR.TUMS.MEDICINE.REC.1398.458).

Informed Consent

All participants in the study were under the legal age of consent. They and their parents or legal guardians were thoroughly informed about the aims of the research and any potential side effects of the interventions. Written informed consent was obtained from the parents or legal guardians of all participants before their involvement in the study.

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Conflict of Interest

None

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