

Preprint of a study on resting-state brain functional networks in children with spinal muscular atrophy using near-infrared functional brain imaging

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Abstract

Background Motor dysfunction in children with spinal muscular atrophy (SMA) is caused by degeneration of motor neurons in the anterior horn of the spinal cord. Studies have shown that both brain structure and brain function undergo plastic changes after spinal cord injury; therefore, it is hypothesized that the brain networks of children with SMA may also be altered. Understanding the functional characteristics of the brain in children with SMA can provide additional data support for rehabilitation treatment. **Objective** To investigate the characteristics of resting-state brain functional networks in children with SMA using functional near-infrared spectroscopy (fNIRS). **Methods** Children aged 5–10 years with type 2 SMA who were admitted to the Department of Rehabilitation Medicine of the Third Affiliated Hospital of Zhengzhou University for rehabilitation treatment from January to July 2024 were enrolled as the SMA group ($n = 23$). Age-matched healthy children aged 5–10 years who volunteered to participate during the same period served as the control group ($n = 23$). fNIRS was used to record cerebral oxygenation signals in the bilateral frontopolar cortex, dorsolateral prefrontal cortex, temporal lobe, Broca's area, and motor areas in both the SMA and control groups during the resting state. An independent-samples t-test was used to compare the functional connectivity matrices and network measures between the two groups, including global efficiency, local efficiency, nodal efficiency, nodal local efficiency, and clustering coefficient. **Results** Brain functional connectivity in children with SMA was stronger than that in the control group ($t = 4.996$, $P < 0.001$), mainly located in the temporal lobe and dorsolateral prefrontal cortex. In terms of global network properties, there was no statistically significant difference in global efficiency between the SMA and control groups ($t = 1.688$, $P > 0.05$); however, local efficiency in the

SMA group was higher than that in the control group ($t = 2.189$, $P = 0.037$). Regarding nodal properties, nodal efficiency in the premotor and supplementary motor areas was higher in the SMA group than in the control group ($t = 2.266$, $P = 0.031$), and the clustering coefficient ($t = 2.177$, $P = 0.038$) and nodal local efficiency ($t = 2.187$, $P = 0.037$) in the frontopolar region were also higher than those in the control group. Conclusion Resting-state brain network functional connectivity is enhanced in children with SMA, and these children may exhibit compensatory mechanisms involving reorganization across multiple brain regions.

Full Text

Study on Resting-state Brain Functional Networks in Children with Spinal Muscular Atrophy Based on Functional Near-infrared Spectroscopy

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Abstract

Background: Motor dysfunction in children with spinal muscular atrophy (SMA) results from degeneration of anterior horn motor neurons. Prior research has demonstrated that spinal cord injury induces plastic changes in both brain structure and function. Based on this, it is hypothesized that children with SMA may also exhibit reorganization within brain networks. Understanding the functional features of the brain in children with SMA may offer additional data support for rehabilitation therapy.

Objective: To investigate resting-state brain network characteristics in children with SMA using functional near-infrared spectroscopy (fNIRS).

Methods: Children aged 5-10 years with SMA type 2 who were admitted to the Department of Rehabilitation Medicine of the Third Affiliated Hospital of Zhengzhou University from January to July 2024 were enrolled as the SMA group ($n=23$). Age-matched healthy children who volunteered during the same period were recruited as controls ($n=23$). fNIRS was used to record cerebral oxygenation signals from the bilateral frontal poles, dorsolateral prefrontal cortex (DLPFC), temporal lobes, Broca's area, and motor cortex during rest.

Independent-samples t-tests were applied to compare group differences in functional connectivity matrices and graph-theoretical network metrics including global efficiency, local efficiency, nodal efficiency, nodal local efficiency, and clustering coefficient.

Results: The SMA group exhibited stronger functional connectivity than the control group ($t=4.996$, $P<0.001$), primarily located in the temporal lobe and DLPFC. Regarding global network metrics, no significant difference in global efficiency was found between the SMA and control groups ($t=1.688$, $P>0.05$). However, local efficiency was significantly higher in the SMA group compared with controls ($t=2.189$, $P=0.037$). For nodal metrics, the SMA group showed greater nodal efficiency in the primary motor cortex and supplementary motor area ($t=2.266$, $P=0.031$). Additionally, both the clustering coefficient ($t=2.177$, $P=0.038$) and nodal local efficiency ($t=2.187$, $P=0.037$) were significantly higher in the frontopolar cortex compared with the control group.

Conclusion: Children with SMA exhibited enhanced functional connectivity within the resting-state brain network, and they may have a compensatory mechanism involving reorganization of multiple brain regions.

Keywords: Spinal muscular atrophy; Functional near-infrared spectroscopy; Functional connectivity; Reorganization; Neuroplasticity

1. Materials and Methods

Spinal muscular atrophy (SMA) is a recessive genetic disorder caused by mutations in the survival motor neuron 1 (SMN1) gene on chromosome 5, leading to reduced expression of SMN protein. This deficiency results in degeneration of anterior horn motor neurons in the spinal cord, causing progressive denervation, muscle atrophy, and weakness. SMA primarily affects motor function and respiratory capacity, with skeletal and gastrointestinal systems becoming involved as the disease progresses, severely compromising quality of life and imposing substantial burdens on families and society. Therefore, developing early intervention and treatment strategies for SMA is crucial for promoting functional recovery and improving quality of life.

Motor impairment is the most severe manifestation in children with SMA, and numerous studies have demonstrated a close relationship between motor function and brain network characteristics. Brain networks are typically divided into multiple subnetworks that gradually mature during childhood development and exhibit dynamic interactions across different tasks and states. Research has confirmed that SMN gene expression is not limited to the anterior horn of the spinal cord but is widely distributed throughout the central nervous system.

Investigating the characteristics of brain functional networks in children with SMA and understanding their relationship with functional status is essential for promoting recovery. Functional near-infrared spectroscopy (fNIRS) is an

emerging non-invasive brain imaging technique that indirectly reflects neuronal activity by monitoring changes in cerebral oxygenated hemoglobin (HbO₂) and deoxygenated hemoglobin (HbR) concentrations in the cerebral cortex. Previous fNIRS studies on brain networks following spinal cord injury have made preliminary progress, demonstrating that both brain structure and function undergo plastic changes after injury. Graph theory, which models the brain as a network of nodes and edges, has proven effective in evaluating both healthy and clinical populations. Clarifying the mechanisms underlying sensory and motor deficits and potential recovery capacity is a critical factor influencing rehabilitation decisions and outcomes. However, no studies have employed fNIRS to investigate brain network changes in children with SMA. This study aims to explore the clinical significance of fNIRS in assessing brain function in children with SMA, providing additional data support for identifying novel therapeutic targets.

1.1 Study Participants

Children with SMA type 2 aged 5-10 years who were admitted to the Department of Rehabilitation Medicine of the Third Affiliated Hospital of Zhengzhou University between January and July 2024 were enrolled as the SMA group (n=23). Healthy children aged 5-10 years who volunteered during the same period served as the control group (n=23). This study was approved by the Ethics Committee of the Third Affiliated Hospital of Zhengzhou University (Approval No: 2023-309-01).

Inclusion criteria for the SMA group: (1) Onset between 6-8 months after birth, maximum motor function achieved independent sitting, and genetically confirmed 5q SMA; (2) Age 5-10 years, right-handed (according to Edinburgh Handedness Inventory); (3) Capable of independent communication, with guardian consent and signed informed consent form.

Exclusion criteria for the SMA group: (1) Severe cardiopulmonary disease that would preclude data collection; (2) Skull defects or unhealed head wounds; (3) Inability to cooperate with data collection.

Inclusion criteria for the control group: (1) Healthy children of hospital staff with normal development, no history of traumatic brain injury, and no family genetic disorders; (2) Age 5-10 years, right-handed (according to Edinburgh Handedness Inventory); (3) Informed consent from both children and guardians.

Exclusion criteria for the control group: (1) Scalp infection or damage preventing detection; (2) Inability to cooperate with data collection.

1.2 Research Methods

1.2.1 fNIRS Data Acquisition fNIRS data were acquired using a multi-channel continuous-wave near-infrared optical imaging system (BS-3000, Wuhan

Zilian Hongkang, China) with a sampling frequency of 20 Hz and wavelengths of 690 nm and 830 nm. The fiber-optic cap, positioned according to the international 10-10 EEG system standard, symmetrically arranged 16 detectors and 16 light sources across the bilateral frontal, parietal, and temporal lobes, forming 44 channels. The specific channel layout and corresponding brain regions are shown in [Figure 1: see original paper]. The cap was symmetrically placed on participants' heads using the nasion, inion, and left/right preauricular points as anatomical landmarks. Participants rested in a quiet, dark, soundproof room with eyes closed but remaining awake, avoiding structured thinking for 230 seconds to obtain resting-state fNIRS data.

1.2.2 Data Preprocessing Data preprocessing was performed using the Homer2 toolbox in MATLAB: (1) The first and last 15 seconds of data were removed to obtain stable signals; (2) A first-order filter was applied to eliminate slow drifts; (3) The TDDR algorithm corrected for head motion artifacts; (4) An infinite impulse response (IIR) filter retained low-frequency neural activity between 0.01-0.08 Hz; (5) Noise was removed from neural recordings using regression. Based on the modified Beer-Lambert law, raw light intensity changes were converted to HbO₂ and HbR concentration changes. Since HbO₂ signals have better signal-to-noise ratios and are more sensitive to regional cerebral blood flow changes than HbR signals, only HbO₂ signals were analyzed in this study.

1.2.3 Brain Network Construction and Analysis Brain networks were constructed using the NIRS_{KIT} toolbox in MATLAB. fNIRS channels were defined as nodes, and functional connections between nodes as edges, generating a 44×44 functional connectivity matrix. Pearson correlation coefficients (r - values) were calculated between HbO₂ time series for each channel pair, representing functional connection strength. To approximate normal distribution and stabilize variance, r -values were Fisher-transformed into Z-scores, which were then thresholded to create binary matrices. NIRS_{KIT} was used to analyze brain network functional connectivity strength. In this study, brain functional networks were constructed across a sparsity range of 0.4-0.9 with intervals of 0.05.

A series of graph-theoretical metrics were used to characterize resting-state fNIRS functional network properties. Definitions and significance of each metric are as follows: **Global efficiency** represents the average of all nodal efficiencies, measuring information integration and transmission efficiency across the network. **Local efficiency** is the average of all nodal local efficiencies, with higher values indicating stronger network fault tolerance. **Nodal efficiency** is the average connection efficiency between a single node and all other nodes, reflecting its participation in global integration. **Nodal local efficiency** measures the connectivity effect of a node's neighbors, with higher values indicating less disruption to information transmission in the neighbor network when that node is removed. **Clustering coefficient** is the ratio of actual edges between

neighbor nodes to the maximum possible edges, reflecting local information integration efficiency. The Brain Connectivity Toolbox (BCT) was used for network parameter analysis, with all network metrics calculated in the GRETNA toolbox.

1.3 Statistical Analysis

All statistical analyses were performed using SPSS 26.0. Continuous variables conforming to normal distribution were expressed as $(\bar{x}\pm s)$ and compared between groups using independent-samples t-tests with false discovery rate (FDR) correction. Categorical variables were expressed as frequencies and compared using χ^2 tests. Statistical significance was set at $P<0.05$.

2. Results

2.1 Demographic Characteristics

This study enrolled 23 children with SMA type 2 (SMA group) and 23 typically developing children (control group). No significant differences were found between groups in age, sex, height, or weight ($P>0.05$).

2.2 Brain Functional Network Connectivity Characteristics

Compared with the control group, the SMA group demonstrated significantly stronger functional connectivity [SMA group mean Z-score representing functional connectivity strength: (0.43 ± 0.07) vs. control group : (0.30 ± 0.05) , $t=4.996$, $P<0.001$]. After FDR correction, these enhanced connections were primarily located in the temporal cortex and dorsolateral prefrontal cortex. Functional connectivity matrices for both groups are shown in [Figure 2: see original paper]A and 2B, with circular plots of characteristic path lengths at a threshold of 0.4 displayed in [Figure 2: see original paper]C and 2D.

2.3 Global Network Metrics

No significant difference in global efficiency was observed between the SMA and control groups ($t=1.688$, $P>0.05$). However, local efficiency was significantly higher in the SMA group compared with controls ($t=2.189$, $P=0.037$).

2.4 Nodal Network Metrics

Nodal efficiency: The SMA group showed significantly greater nodal efficiency in the primary motor cortex and supplementary motor area compared with controls ($t=2.266$, $P=0.031$).

Clustering coefficient and nodal local efficiency: Both the clustering coefficient ($t=2.177$, $P=0.038$) and nodal local efficiency ($t=2.187$, $P=0.037$) were

significantly higher in the frontopolar cortex in the SMA group compared with the control group .

3. Discussion

Disease-modifying drugs such as nusinersen and rehabilitation therapy are widely used in children with SMA, but long-term treatment effects are not always significant and impose substantial financial burdens on families. Therefore, developing efficient and economical rehabilitation protocols is critically important. This study is the first to use fNIRS to evaluate resting-state brain functional network characteristics in children with SMA. The results revealed enhanced functional connectivity in temporal and dorsolateral prefrontal regions, along with differences in graph-theoretical metrics including local efficiency, nodal efficiency in specific regions, clustering coefficient, and nodal local efficiency. These findings suggest that brain networks in children with SMA may undergo functional reorganization across multiple regions, providing new evidence for developing appropriate rehabilitation strategies.

3.1 Functional Connectivity Changes in Children with SMA

The spinal cord serves as the conduit for information exchange between the brain and body, and its damage disrupts sensory and motor signal transmission, limiting neurological recovery. Functional connectivity reflects temporal correlations in neural activity between different brain regions, revealing the brain's intrinsic structural networks. Previous studies have demonstrated significantly increased functional connectivity across multiple regions of the motor network in spinal cord injury patients. For example, Hou et al. found enhanced functional connectivity within the motor network, including primary sensorimotor cortex, premotor cortex, supplementary motor area, thalamus, and cerebellum, in spinal cord injury patients. While the pathological mechanisms differ between spinal cord injury and SMA, both conditions involve interruption of descending motor commands from the cortex due to anterior horn motor neuron degeneration, potentially sharing similar compensatory mechanisms in response to motor dysfunction.

Our study found that children with SMA exhibited stronger functional connectivity in the resting-state brain network compared with healthy children, particularly in the temporal lobe and dorsolateral prefrontal cortex. The temporal lobe is involved in language, memory, and emotional processing, while the dorsolateral prefrontal cortex participates in working memory, attentional control, complex decision-making, behavioral inhibition, and cognitive emotion regulation, serving as a command center for higher cognitive functions. Research has identified a dorsal auditory processing pathway connecting primary auditory cortex through the temporal plane of parietal cortex to the dorsolateral prefrontal cortex, supporting auditory perception-motor signal transmission. Studies in

stroke and traumatic brain injury patients suggest that a major functional reorganization strategy involves recruiting additional motor areas to compensate for insufficient motor output from primary sensorimotor cortex. We hypothesize that the enhanced functional connectivity observed in temporal and dorsolateral prefrontal regions in children with SMA may represent a compensatory mechanism for motor impairment, possibly reflecting enhanced emotional and behavioral regulation demands associated with disease-related stress and challenges. These connectivity changes reflect the brain's neuroplasticity in response to motor system damage.

3.2 Network Parameter Changes in Children with SMA

Graph theory provides a mathematical framework for mapping different patterns of regional structural and functional connectivity in a non-invasive manner. Graph-theoretical analysis has been used to characterize topological alterations after spinal cord injury and reveal pathophysiological mechanisms of brain plasticity. To characterize the topological properties of brain networks in SMA, we analyzed common network parameters including clustering coefficient, nodal efficiency, and global efficiency.

Our results showed that local efficiency was higher in children with SMA compared with controls. Increased local efficiency may reflect brain network reorganization, whereby the brain enhances connections between nodes to improve network fault tolerance. This reorganization may represent an adaptive response to anterior horn cell damage, maintaining or restoring partial function. While Alizadeh et al. found no significant differences in local or global efficiency between chronic spinal cord injury patients and healthy controls, our divergent results may be attributed to the typically long disease course in SMA patients. The chronic nature of motor dysfunction may drive adaptive changes in brain networks to compensate for disease-induced functional deficits.

In this study, increased nodal efficiency in the primary motor and supplementary motor areas in children with SMA suggests greater involvement of motor regions in global information integration and processing. This may represent a strategy to preserve motor function by optimizing local information transmission in response to SMA-related motor dysfunction. Increased clustering coefficient and nodal local efficiency in the frontopolar cortex reflect compensatory mechanisms in language production, tool use, and behavioral planning, likely because children with SMA require enhanced social communication, tool use, and planning abilities to compensate for motor impairments. These findings demonstrate the brain's self-regulatory and adaptive capacity in the face of chronic neurological injury.

3.3 Study Limitations

This study has several limitations: (1) The relatively small sample size may limit generalizability, and future studies should recruit larger samples to verify

stability and reproducibility. (2) This study focused exclusively on children with SMA type 2; further investigation of functional networks across different SMA subtypes is needed. (3) We only analyzed resting-state functional network changes; task-state network characteristics warrant further exploration. As this is the first application of fNIRS technology to SMA research, additional studies are urgently needed to further characterize brain functional network features in this population.

In summary, this study demonstrates that fNIRS can effectively characterize brain functional network features in children with SMA, potentially providing valuable data support for identifying novel therapeutic targets.

Author Contributions: NIU Guohui designed the study, provided guidance and funding, and took responsibility for the manuscript. QU Nannan implemented the study, collected and analyzed data, and drafted the manuscript. ZHANG Xiaoli provided research guidance and manuscript revision. ZHANG Mengmeng, WANG Doudou, and WANG Xin collected and organized data. ZHU Dengna performed data analysis and provided guidance and manuscript revision.

Conflict of Interest: The authors declare no conflicts of interest.

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