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Title: Decreased Functional and Structural Connectivity is Associated with Core Symptom Improvement in Children with Autism Spectrum Disorder After Mini-basketball Training Program

Year: 2023

Version: Accepted version (Final draft)

Decreased overconnectivity associated with improved core symptoms in children with Autism Spectrum Disorder in view of brain function and structure after Mini-Basketball Training Program

Abstract

Purpose: Although exercise intervention has been proven helpful for improvement in core symptoms of Autism Spectrum Disorder (ASD), few studies examined the neural mechanisms of change following exercise intervention. In this study, we focus on brain response following a 12-week mini-basketball training program (MBTP).

Methods: We applied individual analysis for children with ASD aged 3-12 years (experiment group (EXP), N = 30, control group (CON), N = 20) to investigate alterations in functional and structural morphological network, as well as their associations with change in core symptom.

Results: EXP showed decreased positive functional connectivity (FC) within sensorimotor network (SM) as well as between SM and salience network, and increased negative FC between SM and dorsal attention network. In terms of morphological brain network, we found a subcortical-cortical network with decreased connectivity. More importantly, changes in brain were associated with core symptom of ASD. Furthermore, K-means clustering in all children showed the same associations between change in brain and improvement in social deficits as test for group-level.

Conclusion: These findings highlight the effectiveness of MBTP intervention in improving core symptom and decreasing overconnectivity in both structure and function networks, promoting it to neurotypical development. In addition, it's instructive for the development of more targeted and individualized intervention strategy.

Keywords: Autism Spectrum Disorder (ASD); exercise intervention; functional connectivity; morphological brain network; subcortical-cortical network; K-means

Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by social interaction deficits as well as repetitive and stereotyped behavior (American Psychiatric Association, 2013). Despite high prevalence of ASD, the exact etiology is still unclear. Thus, one of the main therapies at present is behavior intervention, including behavior management therapy, social skill training and cognitive behavior therapy, to help reduce common characteristics of ASD (Hynes & Block, 2022).

Physical exercise as a complement to other treatments for maximizing the effect of intervention is receiving more and more interests. What is more, physical exercise (e.g., swimming, cycling, jogging and basketball) has been proven to be helpful for improving social skills, social cognition and social communication (Hynes & Block, 2022; K. Cai et al., 2020; J.-G. Wang et al., 2020; Healy et al., 2018; Howells et al., 2019). Among these physical training interventions, basketball training is seen as a promising intervention featured as team participant, which provides more opportunities on social interaction and social communication for players in the team (Howells et al., 2019; Sowa & Meulenbroek, 2012). Furthermore, early intervention is crucial for the development of nervous system, including the formation of synapses and myelination (Khundrakpam et al., 2016). Hence, we implemented the 12-week mini-basketball training program (MBTP) for children with ASD.

Previous studies mainly revealed the effect of physical exercise on social deficits and execution function (Healy et al., 2018; Hynes & Block, 2022; J.-G. Wang et al., 2020), while few examined brain mechanism accompanied with improved core symptoms. Understanding brain mechanism is essential for developing targeted interventions. (K. Cai et al., 2020) found that children with ASD showed higher fractional anisotropy (FA) in the body of corpus callosum, right cerebral peduncle and left superior front-occipital fasciculus in terms of white matter integrity (WMI) and increased WMI following MBTP. In addition, these altered metrics were associated with improvement in social communication. (Yu et al., 2021) reported increased effective connectivity in medial prefrontal cortex related to change in social responsiveness scale-2 (SRS-2) score after MBTP. However, these studies only focused on single brain regions and single-modality analysis.

In neuroimaging studies, increasing evidence suggests that two core symptoms of ASD is associated with atypical structural and functional networks rather than single region of the brain (Cardon et al., 2017; Nomi & Uddin, 2015). (Uddin et al., 2013) reported hyperconnectivity within salience and motor networks in ASD and the salience network was related to restricted and repetitive behaviors. Several studies reported atypical functional connectivity involving sensorimotor networks in children with ASD and association with social impairment in ASD (Chen et al., 2018; Supekar et al., 2013; Wang et al., 2021). Abnormal structural brain network between subcortical regions in ASD associated with social cognition was also found, suggesting subcortical structures plays a major role in social behavior in ASD (Duan et al., 2020). Inspired from these observations, improved core symptoms after physical training intervention may be related to altered functional and structural networks in ASD.

In this study, we applied advanced individual functional and structural analysis to reveal the neural mechanisms of MBTP intervention mainly on functional and structural networks, and the associations between brain metrics changes and core symptoms for children with ASD. To construct individual-based functional networks and structural morphological networks, individual-specific parcellation developed by (D. Wang et al., 2015) and similarity in regional morphology developed by (Kong et al., 2014) were used in this study. Functional connectivity was calculated using individual-specific parcellation, taking variability of functional brain organization across individual into account (Mueller et al., 2013). And the individual-specific functional connectome have been proven more robust performance in predicting symptom scores in some psychiatric disorders (Fan et al., 2021; M. Li et al., 2019; D. Wang et al., 2020). (Kong et al., 2014) proposed to estimate interregional morphological connectivity by using Kullback-Leibler divergence among different brain regions to construct individual-based structural brain networks. Compared with main studies of structural covariance networks at group-level (Alexander-Bloch et al., 2013), this method preserved the specificity of individual. Further, prevailing test for group-level difference between MBTP and control may only detect common and shared inter-group differences, largely ignoring inter-individual variability. In order to reveal the associations between brain metrics changes and core symptoms for children with ASD, both group difference testing to reveal the effects of MBTP and K-means analysis to identify group with similar profiles across multiple functional and structural features were applied in this study. We speculated that MBTP improved brain metrics in ASD, which related to improved core symptoms.

Methods

Participants

This study included 50 children (aged 3-12 years group; 30 children in the experiment group (EXP) (age: 6.53 ± 2.07, male/female: 26/4) and 20 children in the control group (CON) (age: 6.03 ± 1.97, male/female: 17/3) diagnosed with ASD by DSM-5 criteria (Association American Psychiatric, 2013) recruited from Chuying Child Development Center and Starssailor Education Institution in Yangzhou, China. Participants were excluded if they: (1) involved in structured exercise program in the past 6 months; (2) had a history of substance abuse or dependence in the last 6 months; (3) co-morbid psychiatric or neurological disorders; (4) impaired in visual and/or auditory; (5) had a history of head trauma; (6) had medical contraindications to exercise. The study was approved by the Ethics and Human Protection Committee of the Affiliated Hospital of Yangzhou University, and complied with the ethical standards of the Helsinki declaration.

Mini-Basketball Training Program and Behavioral Measurements

Children in CON kept behavior rehabilitation program set by institutions and did not participant in other sports-related activities. Children in EXP underwent an additional 12-week mini-basketball training program (MBTP) besides routine behavior rehabilitation program.

MBTP was conducted by two certified physical educators and used a collective teaching model to promote social interaction and communication among participants while parent's participant was strongly encouraged. Each MBTP course consists 40 minutes with four parts including 5-min warm-up activities, then a 20-min basic basketball skill learning, followed by 10-min basketball games and finally 5-min cool-down activities. And duration of MBTP is 12-week. More details of the intervention program, please refer to the articles (K. Cai et al., 2020; J.-G. Wang et al., 2020).

We obtained behavior measurements at the beginning and end of MBTP. And demographic information (age, sex and body mass index (BMI)) were obtained at baseline. Core symptom of ASD was assessed by the Social Responsiveness Scale-2 (SRS-2) which is a 65-item scale deficits measurement in social behavior associated with ASD and is filled out by parents, and Repetitive Behavior Scale (RBS-R) which is divided into six dimensions to assess restricted and stereotypical behavior. In these three scales, higher scores represent more severe ASD symptoms.

Data Acquisition

Participants were scanned within 3 days before and after the MBTP intervention and we obtained acquisitions at baseline and at endpoint. To avoid excessive head motion, participants were sedation with 10% chloral hydrate, which are proven to be safe and are approved by family members (Nordahl et al., 2016).

MRI data were acquired using a 3.0 T GE scanner (GE Discovery MR750w 3.0T, Chicago, United States) in the Affiliated Hospital of Yangzhou University. fMRI were collected with echoplanar imaging (EPI) sequence using two acquisition parameters:

(1) repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, timepoint = 240, flip angle (FA) = 90°, matrix size = 64 × 64, field of view (FoV) = 224 mm × 224 mm, voxel size = 3.5 mm × 3.5 mm × 4 mm, slice thickness = 4 mm, slice gap = 5 mm and slice number = 28; (2) TR = 2300 ms, TE = 30 ms, timepoint = 240, FA = 90°, matrix size = 64 × 64, FoV = 224 mm × 224 mm, voxel size = 3.5 mm × 3.5 mm × 4mm, slice thickness = 3 mm, slice gap = 4 mm and slice number = 32. For children with large head circumference, the second parameter was used to obtain better imaging (EXP: 17 subjects; CON:12 subjects). T1-weighted structural images were acquired using a three-dimensional magnetization-prepared rapid acquisition with gradient-echo (MPRAGE) sequence (TR/TE = 7.1/3.2 ms, FA = 12°, Fov = 224 mm × 224 mm and voxel size = 1mm × 1mm × 1mm).

fMRI data preprocessing

Resting-rest fMRI data were preprocessed using FSL package (Woolrich et al., 2001) and FsFast package (http://surfer.nmr.mgh.harvard.edu/fswiki/FsFast). Briefly, the first six volumes were discarded and head motion was corrected with FSL; images with head motion exceeding 3-mm were excluded from further analysis; band-pass filter (0.01-0.08 Hz) was applied and the component that had a strong correlation with global signal was removed from each subject by using a method based on singular value decomposition (SVD).

Structural data were preprocessed using the FreeSurfer software package (http://surfer.nmr.mgh.harvard.edu). The structural and functional images were aligned by boundary-based registration with FsFast. Functional images were registered to Freesurfer template; smoothed with a 6-mm full-width half-maximum (FWHM) smoothing kernel; and then down-sampled to a mesh of 2,562 vertices in each hemisphere.

Construction of individual-specific FC network

Here, we used the iterative algorithms (Wang et al., 2015) to identify individual-specific functional networks to characterize more accurate brain-behavior association. Firstly, the group-level atlas including 18 cortical networks (Wang et al., 2015), which were adapted from the 17 cortical networks based on 1,000 healthy subjects (Thomas Yeo et al., 2011) was registered onto each subject's cortical surface. The individual subject's time courses were calculated by averaging within each network. And each vertex on cortical surface was reassigned to the maximal correlation network. Then individual-specific network atlas was generated by iteratively adjusted network boundary using the inter-subject variability in functional connectivity (Mueller et al., 2013) and signal-to-noise (SNR) distribution. Further, 18×18 correlation maps were obtained by extracting mean time series from the individual-specific atlas and calculating Pearson correlation coefficients (r) in each pair of 18 networks. Finally, the correlation coefficients r maps were converted into Z-score maps using Fisher's r-to-z transform to improve data distribution for statistical analysis.

sMRI data preprocessing

T1-weighted images were preprocessed using FSL pipeline for VBM analysis to obtain grey matter volumes for each subject (Douaud et al., 2007, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM). Briefly, structural images were brain-extracted by FSL's BET and FreeSurfer to remove non-brain tissue better; all brain-extracted images were segmented into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF). Then, segmented GM images were linearly registered to the MNI 152 standard space. GM images in standard space were then averaged together and flipped along x-axis to create a study-specific GM template. All native GM images were then non-linearly registered to the study-specific template. Finally, the resulting GM images were smoothed with a 6-mm full-width half-maximum (FWHM) smoothing kernel.

Construction of individual MBN

Individual morphological brain networks (MBNs) were constructed based on their GM images in which nodes represent brain regions and edges represent the similarity between two regions' morphological measure distributions. Here, we used brain regions defined by automated anatomical labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002), which included 90 brain regions. And network edges were quantified by the symmetric Kullback-Leibler divergence-based similarity (KLS) (Kong et al., 2014; H. Wang et al., 2016) and defined as follows:

$$KLS\ (p,q) = e^{-\sum_{i=1}^{n}(p(i)log\frac{p(i)}{q(i)}+q(i)log\frac{q(i)}{p(i)})}$$

where p and q are grey matter density probability distributions in two different brain regions and estimated using kernel density estimation (KDE) (Botev et al., 2010). N is the number of sampling points ($n = 2^7$ was used in this study, the same as the one in (H. Wang et al., 2016), which was a tradeoff between stability and computational complexity). KLS ranges from 0 to 1, where 1 indicates that p and q have identical distribution. Further, we utilized network-based statistic (NBS) approach (Zalesky et al., 2010) to identify regional brain networks with between-group or within-group significant differences using individual MBN connectivity and explored the topological properties of MNBs based on graph theoretical analysis.

Graph theoretical analysis

All network properties in this study were calculated using GRETNA toolbox (J. Wang et al., 2015) (https://www.nitrc.org/projects/gretna/). The global network metrics included global efficiency (E_{glob}), local efficiency (E_{loc}), clustering coefficient (C_p), characteristic path length (L_p) and small-worldness attributes (σ). E_{glob} and E_{loc} represents network efficiency of transmitting information at global and local level. The clustering coefficient was defined as the likelihood that neighborhoods were connected with each other. Decreased C_p implies reduced efficiency in local information transmission. Small-world attributes is the ratio of normalized C_p (γ) and normalized L_p (λ), which can maximize the efficiency of information transfer at a relatively low cost. At the nodal level, we evaluated nodal degree reflecting the ability of information communication for a given node, nodal efficiency characterizing the efficiency of transferring information in parallel.

Considering that the network metrics has a strong dependence on the network density, we calculated all network metrics under a wide range of sparsity from 5% to 50% with a step of 5% instead of at a specific threshold. And we computed the area under the curve (AUC) from any single threshold for each network metric to provide a comprehensive measure of the topological organization of brain networks.

Statistical analysis

A two-sample t-test was used to test for group difference in age, and a chi-square test was used to test for sex difference between two groups at baseline.

For clinical scales, functional connectivity and graph theoretical metrics, after regressing out the effect of age, sex and site effect using General Linear Model (GLM), we extracted the residual to perform simple effects analysis (baseline EXP vs. endpoint EXP; baseline CON vs. endpoint CON; baseline EXP vs. baseline CON; endpoint EXP vs. endpoint CON). In order to exclude the effect of growth and development and explore the effect of MBTP on brain metrics, a 2 (time: baseline vs. endpoint) × 2 (group: EXP vs. CON) repeated measures ANOVA analysis was performed. All statistical analysis was conducted using R package version 0.8.x (https://CRAN.R-project.org/package=bruceR). Multiple comparisons were corrected by using the false discovery rate (FDR) method (Benjamini & Hochberg, 1995). To further establish an association between altered brain regions and cognitive implications, we performed a meta-analysis using the Neurosynth database (https://neurosynth.org/) (Yarkoni et al., 2011). For both FC and MBN, we generated a map respectively which included all regions with altered functional connections and altered structural connections by MBTP. Next, for each region map, we decoded the cognitive terms and retained the top 30 terms which have substantial relevance.

For MBN connectivity, we utilized Network-Based Statistic (NBS) analysis to examine within-group and between-group changes. The NBS analysis was performed in following steps. First, after regressing out sex, age and site effect, we separately performed a paired t-test within EXP and within CON, a two-sample t-test between EXP and CON (baseline EXP vs. baseline CON; endpoint EXP vs. endpoint CON) and a two-sample t-test between difference of MBN connectivity at endpoint and at baseline calculated in two groups respectively. And we retained the connectivity ($p < 0.05$, uncorrected) as a mask in each t-test step. Then, within this mask, significantly between-group and within-group altered components within these connections were identified by NBS with each connection statistic $T > 3.1$. Finally, a permutation approach was used to estimate the significance of each component (5,000 permutations). We set component significant at $p < 0.05$.

Further, for brain metrics above with significant differences between two groups from baseline to endpoint, we examined their relationship between changes in them with the changes in clinical scores (i.e. SRS Total scores) using Pearson correlation. Both brain metrics and clinical scores were regressed out age, sex and site effect. Particularly, we used the inverse of change in clinical scores (post-pre), hence greater change value in clinical scores indicate greater improvement in social skills or less stereotyped behavior.

K-means analysis

In order to identify groups with similar altered neuroanatomical profile and examine association between altered brain metrics and improvement of core symptoms, we conducted K-means clustering (1000 iterations) across functional and structural brain metrics altered by MBTP in the above analysis in all children. The optimal number of clusters (k = 1-5) was assessed by the silhouette criterion based on a squared Euclidean distance function. For each individual, change in each brain metric from baseline to endpoint was calculated. Then, we performed two-sample t-test to investigate differences in clinical scores and brain metrics across clusters. Multiple comparisons were corrected by using the false discovery rate (FDR) method.

Result

Demographic and clinical characteristics

30 ASD children from EXP and 20 ASD children from CON were included in the study. Demographic characteristics, including age and sex, didn't significantly differ between two groups at baseline (Supplementary Table 1).

We first examined the interaction between group and time in clinical scores including social communication and stereotyped behavior measured by SRS, RBSR total scores as well as their subscale scores. Following MBTP, children in EXP have significantly decreased scores measured by SRS total scores, SRS-Social

Communication scores, SRS-Autistic Mannerisms scores and RBSR-Self-Injurious Behavior scores compared to CON, which means improvement in symptom severity. These changes can be also observed within EXP, while not within CON (Fig. 1a). Clinical characteristics are presented in Supplementary Table 2.

(Fig. 1)

Functional connectivity results

In order to study the effect of MBTP on functional connectivity (FC), we examined the interaction between group and time. Interactions were observed in the within- and between-network functional connectivity of the sensorimotor network (SM) (Fig. 1b, Supplementary Fig. 1a, Supplementary Fig. 1b).

Specifically, following MBTP, children in EXP showed decreased positive connectivity between SM4 and SM2, decreased positive connectivity between SM3 and SN, as well as increased negative connectivity between SM4 and DA1 compared to the control group. Coincidentally, these changes were all observed in EXP at endpoint than at baseline (Fig. 1b). And at baseline, children in EXP showed increased positive connectivity between SM4 and SM2, as well as between SM3 and SN compared to CON, while no significant difference between two groups were found at endpoint.

Using the NeuroSynth meta-analytic database, we found that regions where FC has been changed by MBTP were mainly associated with the function of motor, movement and execution (Supplementary Fig. 1c).

In further exploratory analyses, there were a negative correlation between change of positive FC in SM4 with SM2 and improvement of social skills measured by SRS-Social Cognition scores, as well as a negative correlation between change of positive FC in SM3 with SN and reduction of self-injurious behaviors measured by RBSR-Self Injurious scores. Besides, increased negative connectivity in DA1 with SM4 were positively correlated with improvement of stereotyped behaviors revealed by RBSR Total scores. Here, with regard to the negative connectivity, we displayed the inverse of the connectivity value change (Fig. 1c).

MBN connectivity NBS results

We first examined within-group and between-group changes of MBN connectivity. NBS analysis showed that there was no significantly altered subnetworks from baseline to endpoint within both EXP and CON. No different subnetworks between two groups were observed at baseline. Whereas at endpoint, there was a subcortical-cortical network included 62 nodes and 104 lower MBN connections ($p < 0.001$) in EXP compared to CON, which mainly encompassed subcortical regions (Fig. 2a). In this subcortical-cortical network, regions with top nodal degree were the left caudate, right caudate and left thalamus (Fig. 2b). According to the decoding result, these regions are mainly associated with cognition, like episodic memory, retrieval and memory processes (Fig. 2c).

(Fig. 2)

When investigating the association between change of ASD symptom severity and change of subnetwork connectivity, we found that the mean strength of this subcortical-cortical network revealed by NBS analysis were negatively correlated with the SRS total scores and SRS-social communication scores (Fig. 2d).

Global and nodal topological properties results

Morphological networks in both EXP and CON showed $\gamma > 1$ and $\lambda \approx 1$, indicating a small-world organization (Fig. 3a). There were no significant differences in these global network metrics in CON from baseline to endpoint. Nevertheless, in EXP, there was significant difference in the E_{glob} and L_p in two measures (Fig. 3b, Supplementary Table 3). More specifically, lower E_{glob} and higher L_p were observed at endpoint, compared to the baseline. Besides, there was no significant difference in E_{glob} and L_p in two groups at baseline. While at endpoint, compared to CON, there were lower E_{glob} and higher L_p in EXP. Especially, significant interaction between group and time were observed in these two metrics, which means children in EXP had increased characteristic path length and decreased global efficiency compared to those in CON.

In the exploratory analysis, there was a significant negative correlation between the change of E_{glob} and the change of SRS Total scores. And there was a significant positive correlation between the change of L_p and the change of SRS Total scores (Fig. 3c).

(Fig. 3)

Following the MBTP, children in EXP had decreased nodal degree in the left inferior temporal gyrus (ITG.L), as well as decreased nodal efficiency in the left caudate (CAU.L) and left inferior temporal gyrus (ITG.L) (Fig. 3d, Supplementary Table 3).

Further, interaction results showed that compared to control group, children in EXP had decreased nodal degree and nodal efficiency in ITG.L, with decreased nodal efficiency in CAU.L compared to CON. For nodal degree, change in ITG.L was negatively correlated with the change of SRS total scores. In terms of nodal efficiency, change in ITG.L as well as CAU.L was negatively correlated with the change of SRS total scores (Fig. 3e). These implied that the improvement of social skills associated with decreased nodal degree and efficiency.

K-means result

We conducted K-means clustering analysis with 8 brain metrics (SM4-SM2 FC, SN-SM3 FC, DA-SM4 FC, nodal efficiency in CAU.L and ITG.L, nodal degree in ITG.L, L_p and E_{glob}) affected by MBTP in above analysis in all subjects, and the optimal number of clustering was k = 2 (Fig. 4a). Children in Cluster1 showed significant improvement in SRS-Total, SRS-Communication and SRS-Autistic behavior compared to Cluster2 (Fig. 4d). And proportion of Cluster1 of EXP was also larger than that of CON (EXP-Cluster1: 24 children; EXP-Cluster2: 6 children; CON-Cluster1: 7 children; CON-Cluster2: 13 children), which indicated that more children in EXP showed improvement in core symptoms compared to CON (Fig. 4b, Fig. 4c).

(Fig. 4)

In addition, children in Cluster1 showed significantly more decrease in SN-SM3 FC, nodal efficiency in CAU.L and ITG.L, nodal degree in ITG.L, increased L_p and decreased E_{glob} than children in Cluster2 (Fig. 4e). These results were as the same trend as alterations in EXP compared to CON following by MBTP in test for group-level difference, which both suggested that improvement of social deficits was associated with decreased nodal efficiency in CAU.L and ITG.L, decreased nodal degree in ITG.L, increased L_p and decreased E_{glob}.

Discussion

In this study, we explored the effect of MBTP intervention on brain structure and function in children with ASD using individual-based analysis. To our knowledge, this is the first study to examine neural response of MBTP in terms of both brain structure and function in children with ASD. In addition, we separately conducted test for group-level (EXP VS. CON) difference and test for difference between clusters with similar brain patterns.

Following MBTP, children with ASD had significantly 1) improved social communication and reduced self-injurious behavior; 2) decreased positive functional connectivity within SM (SM2 and SM4), between SM (SM3) and SN, as well as increased negative functional connectivity between SM(SM4) and DA(DA1); 3) decreased morphological subcortical-cortical connectivity centered on subcortical regions; 4) decreased global efficiency, increased characteristic path length, decreased nodal degree in ITG.L, as well as decreased nodal efficiency in ITG.L and CAU.L in MBN. More importantly, we found that changes in these brain metrics were associated with improvement in core symptom of ASD in both group-level analysis and K-means analysis.

Decreased overconnectivity related to SM following MBTP

In recent years, atypical sensory processing and impaired motor processing in ASD has been reported increasingly (Marco et al., 2011; Thye et al., 2018). Further, early motor and sensory abnormalities could lead to social deficit across development (Thye et al., 2018). Sensorimotor network involved input of external stimuli and motor control, which may explain relationship between decreased FC within SM and improvement in social cognition. Overconnectivity within SM and between SM and SN has been reported by previous studies (Cummings et al., 2020; Green et al., 2016; Supekar et al., 2013; Uddin et al., 2013; Wang et al., 2021), which resulted in isolation from neural systems responsible for cognitive processes, thus contributing to core symptoms of ASD (Supekar et al., 2013). Hence, our result implied that the significantly decreased FC between SM4 and SM2 was adjusted following MBTP, which had an association with the improvement of social cognition.

The SN plays a role in determining whether internal or external stimuli are more important to require attention (Menon & Uddin, 2010). Atypical resting-state FC in SN has been consistently reported (Chen et al., 2017; Uddin, 2015; Uddin et al., 2013). The fact that SM is more connected with SN may reflect a lack of functional separation between the two networks and indicate that children with ASD over-allocate attention to basic sensory stimuli rather than to social stimuli (Green et al., 2016). In light of this, interventions that help decrease the salience of extraneous sensory stimuli or increase attention to social stimuli may be particularly helpful for children with ASD (Cummings et al., 2020). The MBTP intervention as a team sport which needs members to support each other, communicate and cooperate with each other is helpful to increase social stimuli to some extent. Thus, FC between SM3 and SN exhibited significantly decreased following MBTP, which had a significant correlation with reduction of self-injurious behavior.

The DA comprises bilateral intraparietal sulcus (IPS) and frontal eye fields (FEF). It modules top-down, goal directed attention (Farrant & Uddin, 2016). We found that negative FC between SM4 and DA1 was significantly increased following MBTP. In typical development, stronger negative FC suggests functionally specialized networks (SM4 and DA1) were more distinct or functionally segregated from each other (Jao Keehn et al., 2019). In addition, we found the increased negative FC had an association with the improvement of stereotyped behavior. This may imply that MBTP enhanced a goal orientation for ASD with less attention to primary sensory, thus affecting attention.

As a whole, our finding demonstrated that MBTP improved core symptom of ASD and modulated atypical functional overconnectivity involving SM, SN, DA.

Decreased MBN overconnectivity in subcortical-cortical network

Following MBTP, children with ASD exhibited decreased MBN connectivity in a subcortical-cortical network, which mainly centered on subcortical regions including left thalamus and both caudate, and connecting to prefrontal, frontal, parietal and occipital lobes.

Regions in subcortical system like thalamus as a relay station for sensory inputs to cerebral cortex circuits, basal ganglia for regulation in motor control and amygdala for emotional perception and regulation were aberrant in ASD (Duan et al., 2020; Leisman et al., 2014). Thalamus and caudate are main regions in CSTC circuitry (Stein et al., 2019; van den Heuvel et al., 2016), which plays an important role in sensorimotor, cognition and motivation process. Previous studies have reported over subcortical-cortical connectivity in children with ASD associated with symptom severity (He et al., 2021; Maximo & Kana, 2019), suggesting that subcortical-cortical abnormality may play a critical role in the neurobiology of ASD.

In addition, we found that change of mean connectivity in the subcortical-cortical network was associated with improvement in social communication and social skills, which indicated that MBTP improved overconnectivity in MBN subcortical-cortical network.

Increased characteristic path length and decreased global efficiency

Abnormal brain network topology in ASD has been widely reported (Harlalka et al., 2018; Lewis et al., 2014; S.-J. Li et al., 2018; Rudie et al., 2013) with inconsistent findings. A study in 24-month-old ASD infants showed reduced global and local efficiency, supporting the under-connectivity theory of ASD (Lewis et al., 2014). In contrast, another study in adolescents with ASD reported the higher global efficiency and lower local efficiency in functional networks (Rudie et al., 2013). Specially, (S.-J. Li et al., 2018) reported a decreased characteristic path length, increased global efficiency, and increased clustering coefficient in preschool children with ASD based on the graph analysis of diffusion-tensor imaging data, which is similar to our results. Randomly connected networks tend to have decreased characteristic path length suggesting that possibility that higher global efficiency may simply reflect a more random distribution of edges, thus these studies may provide evidence that brain network with ASD increased randomness in the network compared with typical development (Harlalka et al., 2018; Rudie et al., 2013). We found lower global efficiency and larger characteristic path length in MBN of children with ASD after MBTP and these changes were accompanied by improvement of social deficits, implying that MBTP reduced randomness in ASD brain network and brought it closer to neurotypical brain networks.

Decreased nodal degree and nodal efficiency in ITG.L and CAU.L

Nodal degree in ITG.L and nodal efficiency in ITG.L and CAU.L were significantly decreased following MBTP. Abnormalities in the temporal lobe, a major region that underlies social, emotional and language functions, are associated with communication and speech deficits in ASD (Courchesne et al., 2007). The ITG is involved in visual perception and processing, which are related to transmitting information back and forth and plays a key role in language and emotional cognition (Hillis, 2014). The striatum is a complex of multiple subcortical regions, including the caudate, putamen, and nucleus accumbens. One study investigated shape difference in boys with ASD, which found decreased social skills in ASD associated with a more convex shape of the caudate (Qiu et al., 2010). The larger caudate volume was observed in adolescents with ASD than in control and correlated with ASD social scores (Zuo et al., 2019). (J. Cai et al., 2018) found increased gray matter volume in ITG of low-functioning ASD compared to in control. Furthermore, increased FC between the medial orbital frontal cortex and ITG of preschool boys with ASD was found (Lan et al., 2022). Based on these findings, our results showing decreased nodal degree and nodal efficiency in ITG.L and CAU.L may reflect that MBTP modulated abnormal local overconnectivity involving the ITG and CAU and increased the separation of brain network to make it develop to neurotypical brain network.

In k-means analysis, we aimed to identify children with similar change in brain phenotype and examine association between altered brain metrics and improvements in core symptoms. And results were consistent with our findings in test for group-level difference. The improved group in social deficits had decreased SN-SM FC, nodal degree and nodal efficiency in ITG.L and CAU.L, global efficiency, as well as increased characteristic path length. And two groups with different changes following MBTP may had specific brain patterns and it's important to guide targeted interventions for them.

In conclusion, we demonstrated the effectiveness of MBTP intervention in improving core symptoms of ASD, including deficit in social interaction as well as restricted and repetitive behaviors. By using a multimodal approach, we found that MBTP decreased abnormal overconnectivity involved SM, SN, as well as DA in functional network and overconnecticity in subcortical-cortical network of structural morphological network, which associated with the improvement of core symptoms, promoting its development to typical neuroanatomy. These results emphasize the importance of timely intervention during the critical period of brain plasticity for ASD. Furthermore, brain changes affected by MBTP provide insights of the neural mechanisms of ASD, which is instructive for making more targeted and individualized intervention strategy.

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Figure Captions

Figure 1. Results of behavior improvement and effect on functional connectivity (FC). **a** The bar graph shows mean clinical scores in each group and interaction graph shows the result of interaction between time and group. Pentagram represents experiment group (EXP) and circle represents control group (CON). EXP showed decreased clinical scores, while CON not. After multiple comparison correction, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$. **b** Within and between group difference for EXP versus CON. EXP showed decreased FC related to SM, while CON not. All regions listed didn't pass fdr correction for the multiple comparisons. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$(uncorrected). **c** Correlation between change of FC and change of clinical variables. For change of each child, we controlled effect of age, sex and site effect. Specifically, we inversed change of clinical scores, so value greater than zero means the improvement of symptom, vice versa.

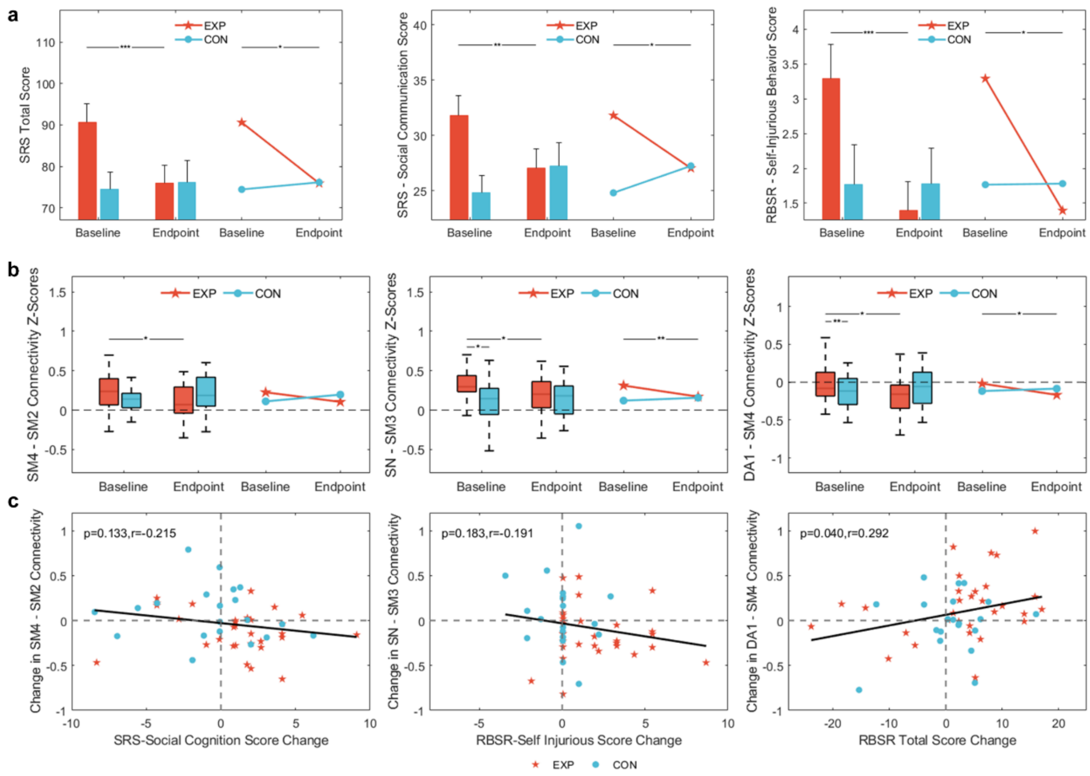
Figure 2. Altered network components identified by NBS analysis following MBTP. **a** A subcortical-cortical network had lower MBN connectivity in experiment group (EXP) than control group (CON) at endpoint, while not at baseline. 90 ROIs from AAL atlas were grouped in 6 different networks as shown in the circle with brain plots and with a different color. **b** BrainNetViewer showed this subcortical-cortical network. Nodes with top nodal degree are left thalamus, left caudate and right caudate in subcortical regions. **c** Cognitive terms associated with regions in which this subcortical-cortical network included. Font Size has been scaled to represent the correlation value for each cognitive term. **d** The scatter graphs show negative correlations between

change of the average MBN connectivity within the subcortical-cortical network and change of social interaction and communication in ASD.

Figure 3. The effect on topological properties. **a** Children in both EXP and CON exhibited $\gamma > 1$ and $\lambda \approx 1$, which are typical features of small-world topology. γ, normalized clustering coefficient; λ, normalized characteristic path length. **b** EXP showed lower global efficiency (E_g) and higher characteristic path length (L_p). **c** Correlation between change of global topological properties and clinical scores are represented. **d** EXP showed lower nodal degree in ITG.L, as well as lower nodal efficiency in ITG.L and CAU.L compared to CON. $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$(corrected). **e** Correlation between change of local topological properties and clinical scores are represented. ITG.L: left inferior temporal gyrus, CAU.L: left caudate.

Figure 4. Result of K-means clustering in all children. **a** The optimal number of clustering in all children. The figure shows that k = 2 was optimal. **b** TSNE project of children in two clusters. Cluster1 represented children with improvement of social deficits. Cluster1 is showed by asterisk. **c** The proportion of two clusters in EXP and CON. **d** Group comparation on behaviors between two clusters. The bolder line represents Cluster1, which showed more improvement on social skills than Cluster2. **e** Group comparation on brain metrics between two clusters. $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$(fdr corrected). We used brain metrics Z-score to display.

Figure 1 top



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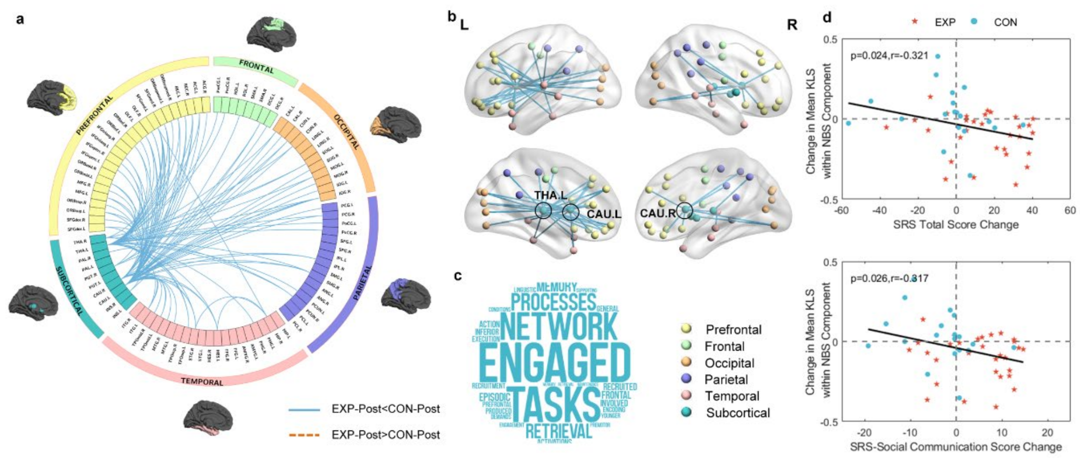

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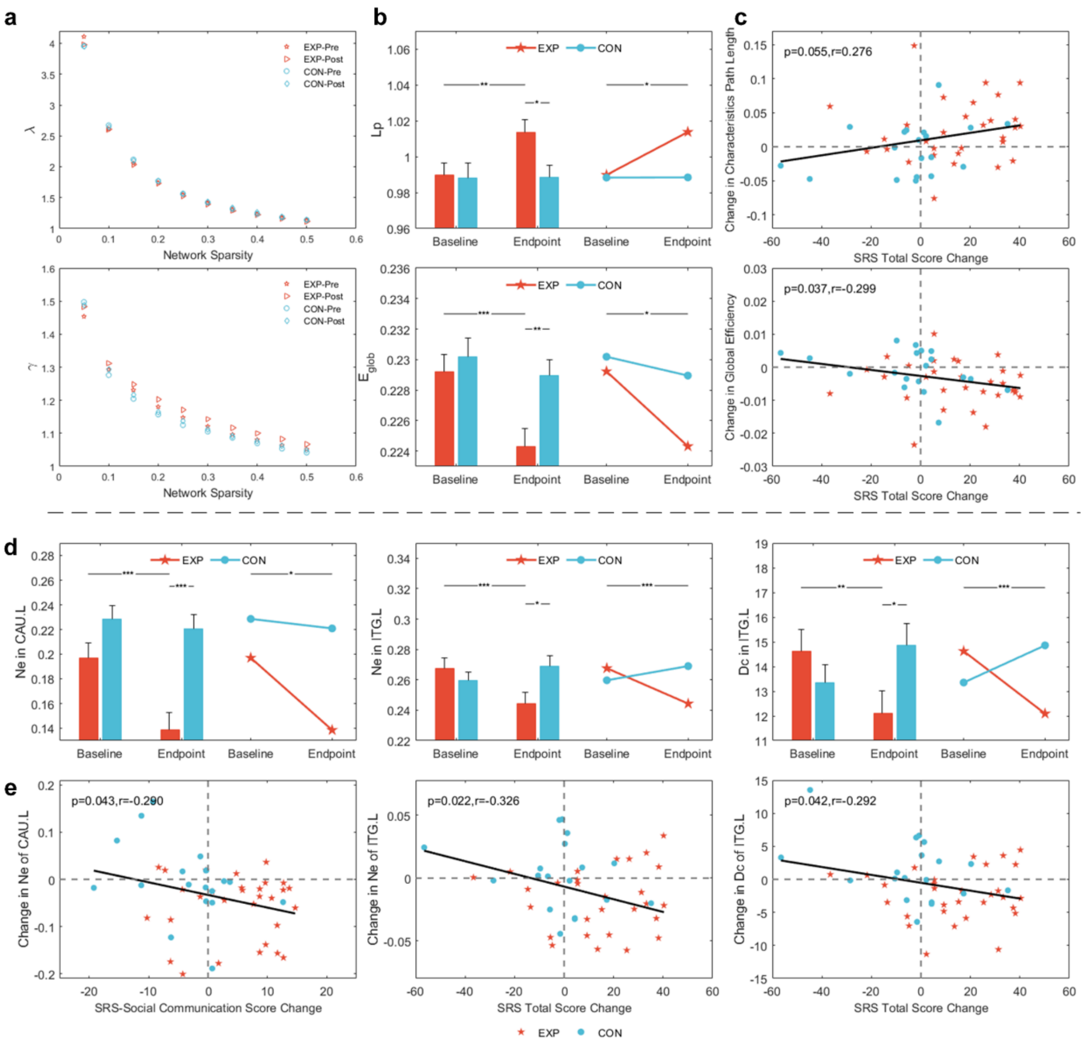

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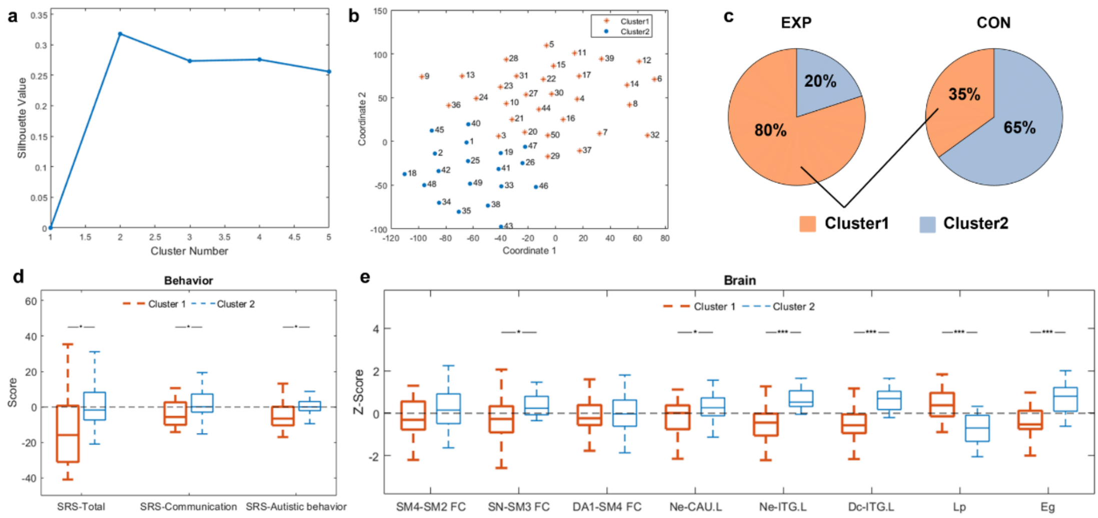

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