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Effects of vitamin D on brain function in preschool children with autism spectrum disorder: a resting-state functional MRI study

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Abstract

Background Previous studies indicate vitamin D impacts autism spectrum disorder (ASD), but its relationship with brain function is unclear. This study investigated the association between serum 25-hydroxyvitamin D [25(OH)D] levels and brain function in preschool children with ASD using resting-state functional magnetic resonance imaging (rs-fMRI), and explored correlations with clinical symptoms.

Methods A total of 226 ASD patients underwent rs-fMRI scanning and serum 25(OH)D testing. Clinical symptoms were assessed using Childhood Autism Rating Scale (CARS) and Autism Behavior Checklist (ABC). Patients were categorized into mild and severe groups based on the CARS, and further divided into normal (NVD), insufficient (VDI), and deficient (VDD) serum 25(OH)D levels. Changes in brain function among these groups were analyzed using regional homogeneity (ReHo), with ABC scores used for correlation analysis.

Results In mild ASD, ReHo increased in the right postcentral gyrus and left precuneus in the VDI and VDD groups compared to NVD, and decreased in the bilateral middle cingulate gyrus and left superior frontal gyrus in the VDD group compared to VDI. In severe ASD, ReHo decreased in the right middle occipital gyrus and increased in the right insula in the VDI group compared to NVD, and increased in the right superior frontal gyrus in the VDD group compared to VDI. Correlation analysis revealed that in mild ASD, ReHo in the right postcentral gyrus was positively correlated with body and object use scores in the NVD and VDI groups, while ReHo in the right middle cingulate gyrus was negatively correlated with relating scores in the VDD and VDI groups. In severe ASD, ReHo in the right insula was positively correlated with language scores in the NVD and VDI groups.

Conclusions ASD patients with lower serum 25(OH)D levels show multiple brain functional abnormalities, with specific brain region alterations linked to symptom severity. These findings enhance our understanding of vitamin D's impact on ASD and suggest that future research may explore its therapeutic potential.

Keywords Autism spectrum disorder (ASD), Vitamin D, Resting-fMRI, Regional homogeneity (ReHo), Preschool children

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Background

The prevalence of autism spectrum disorder (ASD) has significantly increased over recent decades, drawing considerable attention from both the scientific community and the general public [1]. ASD is characterized by a wide range of social, communication, and behavioral challenges, with symptoms and severity varying greatly among affected individuals [2]. The etiology of ASD remains multifactorial, involving a complex interplay of genetic, environmental, and neurobiological factors contributing to its development and manifestation [1]. Among these, the role of nutritional elements, particularly vitamin D, has emerged as an area of interest due to its potential influence on neurodevelopmental outcomes [3].

In addition to its well-known function in calcium homeostasis, vitamin D, a secosteroid hormone, plays a pivotal role in regulating brain homeostasis, neurodevelopment, and neuroprotection [4–8]. The active form of vitamin D, 1,25(OH)2-vitamin D, exerts its effects by binding to its specific ligand, the vitamin D receptor (VDR). VDR is widely distributed throughout the brain, indicating that vitamin D is involved in crucial neurobiological processes [4, 9–12]. Additionally, 223 ASD risk genes are sensitive to vitamin D3, suggesting that vitamin D plays a crucial role in the regulation of ASD gene expression [13]. While some foods contain small amounts of vitamin D, the primary source for most individuals is exposure to ultraviolet B radiation from sunlight. Several studies have indicated that the risk of developing ASD is associated with the amount of solar ultraviolet B exposure [14–16]. Emerging evidence suggests that vitamin D deficiency may be linked to various neurodevelopmental disorders, including ASD [5, 17, 18]. Research conducted on animal models indicates that maternal vitamin D deficiency precipitates persistent alterations in both the structure and function of the offspring brain [19]. Epidemiological studies have suggested a link between vitamin D deficiency during pregnancy and an increased risk of ASD in offspring [20]. Therefore, vitamin D plays an important role in ASD.

25-Hydroxyvitamin D [25(OH)D] is the primary circulating form of vitamin D in the bloodstream and serves as a biomarker for assessing vitamin D levels. A multicenter study in China has revealed that children with ASD exhibit lower serum levels of 25(OH)D than neurotypical children [21]. Furthermore, the study revealed a significant inverse correlation between 25(OH)D levels and the severity of autism symptoms; lower 25(OH)D levels were associated with more severe manifestations of ASD. Previous research has indicated that vitamin D plays a crucial role in modulating neural circuits integral to the core symptoms of ASD, including the social reward and corticostriatal pathways [22]. These neural circuits are essential for processing social interactions and corresponding rewards and are typically impaired in individuals with ASD [23]. Despite these advancements, the precise relationship between vitamin D levels and brain function in individuals with ASD requires further investigation.

Resting-state functional magnetic resonance imaging (rs-fMRI) is a powerful tool for investigating brain function by measuring spontaneous brain activity and functional connectivity. Its ability to collect data without requiring task execution makes it particularly suitable for studies involving children [24]. Regional homogeneity (ReHo) measures the local coherence or synchrony of the blood oxygen level dependent (BOLD) signal between a given voxel and its neighboring voxels [25], reflecting the functional connectivity and information processing efficiency within that region. The rs-fMRI technique has been extensively utilized in the study of ASD [26–28]. In a rs-fMRI study, Zhao et al. [29] identified extensive ReHo abnormalities in adolescents with high-functioning ASD compared to typically developing (TD) controls. They also found that brainstem ReHo was negatively correlated with Autism Behavior Checklist (ABC) total scores and correlation factor scores. Lan et al. [30] observed spontaneous activity changes in multiple brain regions, particularly in visual and language-related regions, in preschool boys with ASD compared to those in TD children. However, no correlation was found between these brain region changes and scores on the Childhood Autism Rating Scale (CARS) or the ABC scale. Although previous studies have revealed changes in brain functional connectivity in children with ASD, research on the relationship between vitamin D and brain function in ASD patients remains relatively scarce. However, studies in other neurological disorders using rs-fMRI have shown that vitamin D is closely associated with functional connectivity across various brain regions, suggesting that vitamin D may have a significant impact on brain function. Lv et al. [31] analyzed the impact of vitamin D status on spontaneous neuronal activity across the whole brain by measuring the fractional amplitude of low-frequency fluctuations (fALFF). They found that lower serum 25(OH)D levels significantly affect the spontaneous activity of neurons in the default mode network (DMN) and visual pathways in patients with Parkinson's disease. Therefore, by examining the resting-state brain function of children with ASD and correlating it with vitamin D levels, we can gain deeper insights into the potential neuroprotective roles of vitamin D and its association with the neural mechanisms underlying ASD.

This study aimed to bridge this gap by employing rs-fMRI to investigate the impact of vitamin D on brain function in children with ASD. In this study, we grouped ASD children based on their serum 25(OH)D levels and

assessed their resting-state brain function using the ReHo method. We hypothesized that ASD patients with varying serum 25(OH)D levels exhibit different ReHo kinetics and that these changes in brain function may correlate with the severity of clinical symptoms. By linking serum 25(OH)D levels with alterations in resting-state brain function, this study aimed to provide new insights into the neurobiological underpinnings of ASD.

Methods

Participants

This study retrospectively analyzed 226 children aged 24–72 months who were first diagnosed with ASD at the First Hospital of Jilin University between January 2022 and July 2023. The diagnosis was made by two associate senior pediatricians based on the DSM-V criteria for the clinical diagnosis of ASD. All the children completed the CARS and ABC assessments, which were administered, scored, and interpreted by professionally trained pediatricians. Fasting serum samples were collected by qualified laboratory technicians following standard protocols. Considering that the severity of the disease can impact brain function, we divided the patients into two groups based on the severity of ASD using the CARS: mild (30–36) and severe (≥ 37). Within each severity group, patients were further categorized into three groups based on serum 25(OH)D levels: normal vitamin D (NVD) > 30 ng/ml, insufficient vitamin D (VDI) 20–30 ng/ml, and deficient vitamin D (VDD) < 20 ng/ml [32]. The exclusion criteria included incomplete clinical data, epilepsy, other neurodevelopmental disorders, structural brain abnormalities, and the use of medications that could affect serum 25(OH)D levels (such as immunosuppressive drugs, corticosteroids, and antiepileptic drugs). We obtained informed consent from the parents or caregivers of the children who participated. The study received ethical approval from the Medical Ethics Committee of the First Hospital of Jilin University (23K195-002).

Behavioral assessment

CARS and ABC are the primary diagnostic and screening tools used for pre-treatment assessment of children with ASD in China. Developed by Schopler et al., CARS provides a structured, observation-based assessment of behaviors associated with ASD across various domains, including social interaction, communication, and repetitive behaviors [33]. Schopler et al. [34] developed the second version of CARS-2 in 2010, which is the version used in this study. The CARS consists of fifteen items, each rated on a scale from 1 to 4, with higher scores indicating greater severity of autistic symptoms. A total score of less than 30 is considered non-autistic, a score of 30–36 indicates mild to moderate ASD, and a score of 37 or higher indicates severe ASD. The ABC is another widely used assessment tool for evaluating ASD symptoms, particularly in children and adolescents. Originally developed by Krug et al., the ABC is a caregiver-reported questionnaire consisting of 57 items designed to assess various aspects of behavior associated with ASD across five domains: sensory, relating, language, social self-help and body and object use [35].

Serum 25(OH)D testing

Blood samples were collected from all study participants under fasting conditions to ensure consistency in vitamin D concentration measurements. The samples were drawn using standard phlebotomy techniques by trained medical professionals and processed within two hours of collection to maintain their integrity. The assessment focused on measuring the serum levels of 25(OH)D, which were determined using liquid chromatography-tandem mass spectrometry (LC-MS/MS; 6470, Agilent Technologies, CA, USA). The quantitation limit and detection limit were 1.2 ng/mL and 0.4 ng/mL, respectively. The intra-day and inter-day precision were 3.22% and 5.64%, respectively. To account for the effect of seasonal variation on vitamin D absorption [36], we divided patients who underwent serum 25(OH)D testing into four groups based on the season of sample collection: spring (March to May), summer (June to August), autumn (September to November), and winter (December to February).

MRI acquisition

The participants in this study were young, necessitating a carefully developed sedation protocol to ensure patient cooperation and minimize motion artifacts. Specifically, 30 min prior to the scanning process, each participant received a sedation solution consisting of 10% chloral hydrate (at a dose of 0.5 ml/kg, not exceeding 10 ml in total) and an equal amount of 0.9% sodium chloride. This mixture was administered via a retention enema. The scan started after the subject was fully asleep. A guardian was required to be present throughout the scanning process. Following the scan, participants were transferred to a designated rest area within the department where they were closely monitored. Most participants regained full consciousness within 30 to 60 min, though recovery time varied depending on individual differences. Monitoring continued until participants were fully awake and stable.

MRI data were collected using a 3.0 Tesla MRI scanner (Ingenia Elition X, Philips Healthcare, Best, the Netherlands). Each participant was positioned supine, with the head stabilized using foam pads to prevent movement, and earplugs were used to prevent sleep disruption during the scan. The parameters for the three-dimensional spoiled gradient-echo (3D-SPGR) sequence were as follows: field of view (FOV) = 226 mm × 226 mm,

repetition time (TR) = 6.6 ms, echo time (TE) = 3.0 ms, flip angle (FA) = 8°, slice thickness = 1 mm, slice number = 150 and voxel size = 1.0 mm × 1.0 mm × 1.0 mm, gap between slices = 0 and scanning time 2 min 29 s. For rs-fMRI scans, the parameters included FOV = 230 mm × 230 mm, matrix = 76 × 76, TR = 983 ms, TE = 35 ms, FA = 70°, package = 2, slice thickness = 4 mm, gap between slices = 0, slice number = 36, voxel size = 3 mm × 3 mm × 4 mm, with a total of 200 volumes acquired and scanning time 6 min 35 s.

Image processing

All processing was performed using the DPARSF 6.0 running on MATLAB R2021A. The following preprocessing steps were applied: (1) conversion of DICOM to NIFTI; (2) remove of the first 10 time points; (3) realignment: All images were realigned to the first volume to correct for head motion, with excessive head movement defined as translation or rotation of more than 3 mm or 3°; (4) coregistration; (5) segmentation: The structural image was segmented into gray matter, white matter, cerebrospinal fluid, bone, soft tissue and air/background; (6) normalization: The functional and structural images were normalized to the Montreal Neurological Institute (MNI) template by Diffeomorphic Anatomical Registration Through Exponentiated Lie (DARTEL) [37], and images were resampled to 3 mm isotropic voxels; (7) regression: Several nuisance covariates, including the linear trend, Friston-24 parameters of head motions [38, 39], and the white matter and cerebrospinal fluid signals, were regressed out from the data; (8) detrending: Linear and quadratic trends were removed to correct for drifts in the time series; (9) temporal filtering: A band-pass filter (0.01–0.08 Hz) was applied to the time series to focus on the frequency range commonly associated with resting-state fluctuations; (10) ReHo: The Kendall's coefficient of concordance (KCC) was calculated among the time series of neighboring voxels (27 voxels) to measure the local synchrony. The ReHo values were then normalized using z-score transformation to obtain zReHo. Finally, spatial smoothing was applied to zReHo using a 6 mm full-width at half-maximum (FWHM) Gaussian kernel to reduce spatial noise.

Statistical analysis

Initially, a chi-square test was used to compare sex and season of blood collection between subgroups with different serum 25(OH)D levels in mild and severe ASD. One-way ANOVA and the Kruskal-Wallis H test were utilized to compare age, total ABC scale scores, and subscale scores among subgroups with different serum 25(OH)D levels within the mild and severe ASD groups. Statistical analyses were performed using IBM SPSS software (IBM, Version 26.0), with statistical significance set at $p < 0.05$.

ReHo was processed using SPM12 (v7219). Differences in ReHo among the three subgroups of patients with different serum 25(OH)D levels were assessed using one-way ANCOVA, controlling for age and sex as covariates. If one-way ANCOVA revealed significant differences, post-hoc tests (two-sample t-tests) were conducted to explore pairwise comparisons, with adjustments for multiple comparisons using the Bonferroni correction. Statistical thresholds were set at $p < 0.001$ for the voxel level and $p < 0.05$ (two-tailed) for the cluster level, with Gaussian random-field (GRF) correction applied to determine statistical significance. If post-hoc tests reveal significant differences in ReHo values of the brain regions between any two groups, the mean ReHo values for these brain regions in both groups will be extracted. Furthermore, Pearson correlation analysis was conducted to clarify the relationship between patients' ReHo values and clinical scale scores. Statistical significance was set at $p < 0.05$.

Results

Participants' demographic characteristics

Table 1 shows the demographic and clinical characteristics of the groups of ASD patients in this study. No

Table 1 Demographic characteristics of all the participants

	Mild ASD			F/X^2	p	Severe ASD			F/X^2	p
	NVD ($n=36$)	VDI ($n=38$)	VDD ($n=38$)			NVD ($n=38$)	VDI ($n=39$)	VDD ($n=37$)		
Age (months), (Mean ± SD)	41.14 ± 6.53	42.87 ± 9.86	43.71 ± 6.85	2.924	0.232[a]	40.53 ± 9.34	40.64 ± 10.67	43.43 ± 8.20	1.129	0.327[a]
Gender, (male/female)	28/8	31/7	27/11	1.210	0.546[b]	27/11	31/8	24/13	2.032	0.362[b]
Season of blood collection, n(%)										
Spring	8 (22.22)	9 (23.68)	12 (31.58)	2.617	0.855[b]	7 (18.42)	12 (30.77)	11 (29.73)	3.897	0.691[b]
Summer	9 (25.00)	12 (31.58)	10 (26.32)			11 (28.95)	9 (23.08)	12 (32.43)		
Autumn	13 (36.11)	9 (23.68)	9 (23.68)			12 (31.58)	8 (20.51)	7 (18.92)		
Winter	6 (16.67)	8 (21.05)	7 (18.42)			8 (21.05)	10 (25.64)	7 (18.92)		

Abbreviations: ASD, autism spectrum disorder; NVD, normal serum 25(OH)D; VDI, insufficient serum 25(OH)D; VDD, deficient serum 25(OH)D; SD, standard deviation; a, one-way ANOVA; b, chi-square test

significant differences were observed in age, sex, or the season of blood collection among subgroups with different serum 25(OH)D levels.

Participants' clinical scale scores

Table 2 shows that the CARS, body concept, sensory, relating, language, social self-help and total scores on the ABC scale were significantly different among subgroups with different serum 25(OH)D levels.

ReHo in the subgroups with different serum 25(OH)D levels in mild ASD

Differences were observed in the ReHo values of brain regions, including the bilateral middle cingulate gyrus, left superior frontal gyrus, right postcentral gyrus, and left precuneus, among the three serum 25(OH)D subgroups of mild ASD patients (Fig. 1a; Table 3). In children with mild ASD, the ReHo values were greater in the right postcentral gyrus and left precuneus in the VDI and VDD groups than in the NVD group (Fig. 1b-c; Table 3) and decreased in the bilateral middle cingulate gyrus and the left superior frontal gyrus in the VDD group compared with the VDI group (Fig. 1d; Table 3).

ReHo values in the subgroups with different serum 25(OH)D levels in severe ASD patients

Differences were observed in the ReHo values of brain regions, including the right middle temporal gyrus, right insula, and right superior frontal gyrus, among the three serum 25(OH)D subgroups of severe ASD patients. In children with severe ASD, the ReHo values increased in the right middle temporal gyrus and right insula in the VDI group compared to the NVD group (Fig. 2b-c; Table 4) and increased in the right superior frontal gyrus in the VDD group compared to those in the VDI group (Fig. 2d; Table 4).

Relationships between the ReHo values and psychopathological characteristics

In mild ASD, we observed a positive correlation between ReHo values in the right postcentral gyrus and body and object use scores in the NVD and VDI groups (Fig. 3a, $r = 0.4577$) and a negative correlation between ReHo values in the right middle cingulate gyrus and relating scores in the VDD and VDI groups (Fig. 3b, r = -0.5285). Furthermore, in severe ASD, we found a positive correlation between ReHo values in the right insula and language scores in the NVD and VDI groups (Fig. 3c, $r = 0.4165$).

Discussion

In this study, we examined brain function abnormalities in children with ASD with different serum 25(OH)D levels using ReHo and further investigated their correlation with symptom severity. We found that as serum 25(OH)D levels decreased, scores on the CARS and the ABC scale, including its subscales, tended to increase, suggesting that serum 25(OH)D levels may influence the severity of ASD. Previous studies have also indicated that vitamin D deficiency exacerbates symptoms in children with ASD and that vitamin D supplementation can improve these

Table 2 Clinical scale scores of all the participants

	Mild ASD			F/H	*p*	Severe ASD			F/H	*p*
	NVD (*n* = 36)	VDI (*n* = 38)	VDD (*n* = 38)			NVD (*n* = 38)	VDI (*n* = 39)	VDD (*n* = 37)		
CARS (Mean ± SD)	32.58 ± 1.65	33.11 ± 1.66	33.87 ± 1.85	5.237	0.007[a]	38.45 ± 1.33	39.62 ± 1.82	40.19 ± 1.91	10.215	< 0.001[a]
ABC										
Body and object use (Median [IQR])	8.00 (6.00, 10.00)	8.50 (4.00, 14.00)	10.00 (7.75, 14.00)	6.306	0.043[b]	9.00 (8.00, 15.50)	12.00 (9.00, 16.00)	14.00 (10.00, 22.00)	6.991	0.030[b]
Sensory (Median [IQR], Mean ± SD)	7.50 (5.00, 9.00)	7.00 (6.00, 11.00)	9.50 (6.75, 12.00)	7.407	0.025[b]	10.05 ± 3.26	11.18 ± 4.05	12.24 ± 3.55	3.398	0.037[a]
Relating (Mean ± SD, Median [IQR])	11.08 ± 5.15	12.76 ± 5.05	14.45 ± 5.19	3.978	0.022[a]	15.00 (12.00, 20.00)	17.00 (14.00, 20.00)	18.00 (16.00, 20.50)	6.714	0.035[b]
Language (Median [IQR])	7.00 (5.00, 10.00)	9.00 (5.75, 11.25)	10.00 (7.75, 11.00)	8.199	0.017[b]	8.00 (7.75, 10.00)	9.00 (8.00, 11.00)	10.00 (8.50, 12.00)	7.241	0.027[b]
Social self-help (Median [IQR], Mean ± SD)	9.00 (7.00, 11.00)	11.00 (8.00, 13.00)	12.00 (9.00, 14.00)	11.956	0.003[b]	11.11 ± 3.376	12.23 ± 3.133	13.08 ± 3.72	3.171	0.046[a]
Total ABC score (Mean ± SD, Median [IQR])	43.39 ± 14.64	48.50 ± 12.49	55.26 ± 13.49	7.170	0.001[a]	53.00 (46.00, 71.50)	59.00 (56.00, 71.00)	70.00 (62.50, 74.00)	12.978	0.002[b]

Abbreviations: ABC, Autism Behavior Checklist; ASD, autism spectrum disorder; CARS, Childhood Autism Rating Scale; IQR, interquartile range; SD, standard deviation; NVD, normal serum 25(OH)D; VDI, insufficient serum 25(OH)D; VDD, deficient serum 25(OH)D; a, one-way ANOVA; b, Kruskal-Wallis H test

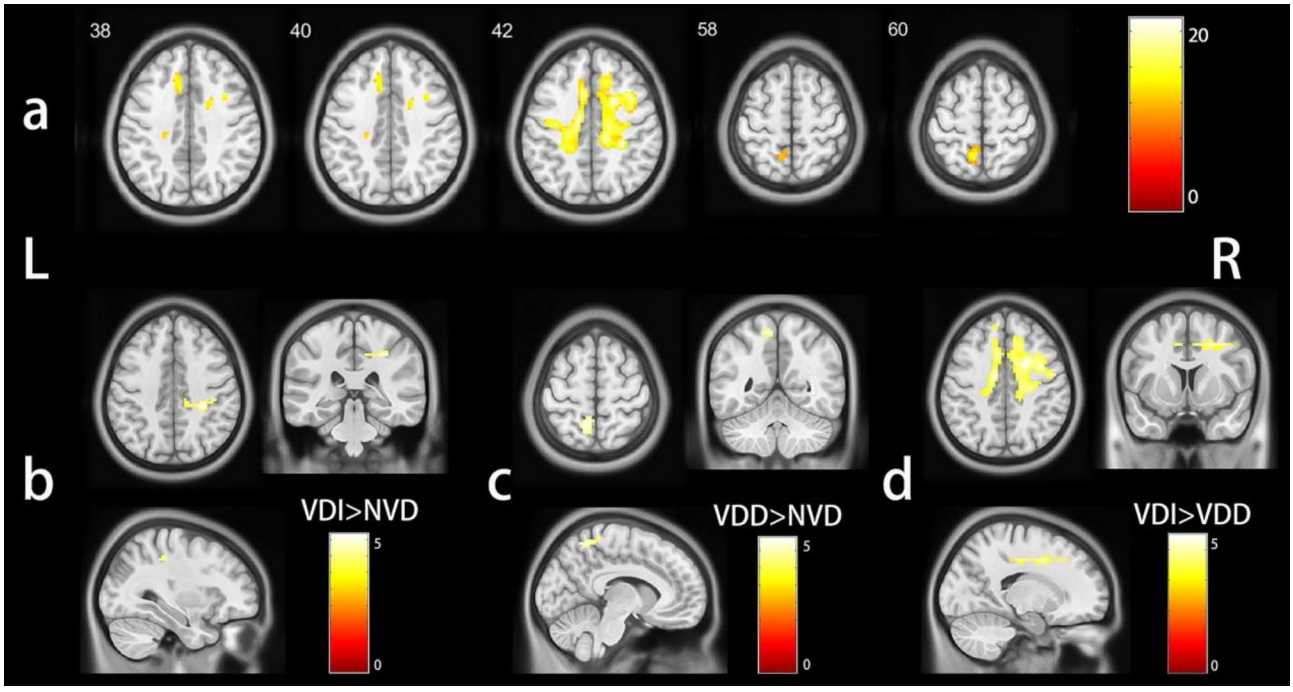

Fig. 1 Brain regions with significantly different ReHo values among the subgroups with different serum 25(OH)D levels in mild ASD. **a**: Clusters showing significant differences in ReHo values among the three subgroups in mild ASD patients. **b**: Clusters showing significant differences in ReHo values between the NVD group and the VDI group. **c**: Clusters showing significant differences in ReHo values between the NVD group and the VDD group. **d**: Clusters showing significant differences in ReHo values between the VDI group and the VDD group. The color bar signifies *F* values in a, and *t* values in b-d. NVD, normal serum 25(OH)D; VDI, insufficient serum 25(OH)D; VDD, deficient serum 25(OH)D; MNI, Montreal Neurological Institute; ReHo, regional homogeneity

Table 3 Regions with significantly different ReHo among subgroups with different serum 25(OH)D levels in mild ASD

Brain regions	MNI Peak			Cluster size	F/t value
	X	Y	Z		
ANCOVA					
Left middle cingulate gyrus	-12	-9	42	116	19.2624
Left superior medial frontal gyrus					
Left superior frontal gyrus, part 2					
Right middle cingulate gyrus	30	-33	42	181	18.6726
Right postcentral gyrus					
Left precuneus	-9	-54	60	47	15.9207
VDI > NVD					
Right postcentral gyrus	30	-33	42	42	4.2589
VDD > NVD					
Left precuneus	-9	-54	60	48	3.9207
VDI > VDD					
Right middle cingulate gyrus	21	6	42	215	4.4383
Left middle cingulate gyrus	-12	-9	42	122	4.3481
Left superior medial frontal gyrus					
Left superior frontal gyrus, part 2					

GRF correction, voxel level: $p < 0.001$, cluster level: $p < 0.05$

Abbreviations: ASD, autism spectrum disorder; NVD, normal serum 25(OH)D; VDI, insufficient serum 25(OH)D; VDD, deficient serum 25(OH)D; MNI, Montreal Neurological Institute; ReHo, regional homogeneity

symptoms [40–43]. We observed altered ReHo in certain brain regions of ASD patients with different serum 25(OH)D levels, suggesting that local neural synchronization and functional connectivity may be affected in the presence of vitamin D deficiency. This finding also implies that the cerebral cortex may be particularly susceptible to vitamin D deficiency, highlighting the important role of vitamin D levels in the functional assessment of neural networks in individuals with ASD.

In children with mild ASD, we found that ReHo increased in the right postcentral gyrus and left precuneus in the VDI and VDD groups compared to that in the NVD group, and decreased in the bilateral middle cingulate gyrus and left superior frontal gyrus in the VDD group compared to the that in VDI group. The postcentral gyrus, located in the parietal lobe, is involved in somatosensory processing, including tactile sensation and proprioception. Decreased ReHo in the postcentral gyrus may indicate altered sensory processing in ASD children with 25(OH)D insufficiency or deficiency. Moreover, we found that the ReHo in the right postcentral gyrus was positively correlated with body and object use scores in the NVD and VDD groups. Therefore, we speculate that vitamin D is associated with sensory processing in individuals with ASD. Clinical randomized controlled trials are needed in the future to confirm this

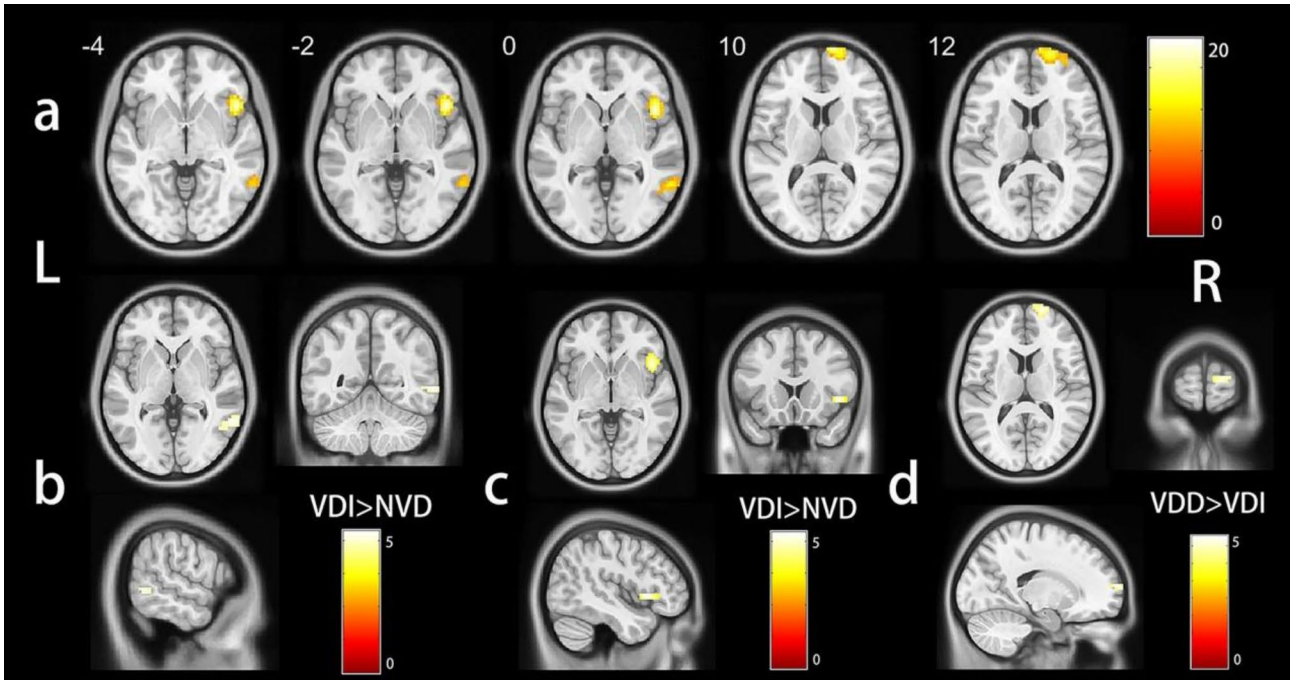

Fig. 2 Brain regions with significantly different ReHo values among the subgroups with different serum 25(OH)D levels in severe ASD. **a**: Clusters showing significant differences in ReHo values among the three subgroups in severe ASD patients. **b** and **c**: Clusters showing significant differences in ReHo values between the NVD group and the VDI group. d: Clusters showing significant differences in the ReHo between the VDI group and the VDD group. The color bar signifies *F* values in a, and *t* values in **b**-**d**. Abbreviations: NVD, normal serum 25(OH)D; VDI, insufficient serum 25(OH)D; VDD, deficient serum 25(OH)D; MNI, Montreal Neurological Institute; ReHo, regional homogeneity

Table 4 Regions with significantly different ReHo among subgroups with different serum 25(OH)D levels in severe ASD

Brain regions	MNI Peak			Cluster size	F/t value
	X	Y	Z		
ANCOVA					
Right middle temporal gyrus	60	-54	0	33	11.7091
Right insula	45	15	0	50	17.3445
Right superior frontal gyrus, part 2	12	72	9	59	15.7076
Right superior medial frontal gyrus					
VDI > NVD					
Right middle temporal gyrus	60	-54	0	32	3.4546
Right insula	45	15	0	44	4.2046
VDD > VDI					
Right superior frontal gyrus, part 2	12	72	9	53	3.9537
Right superior medial frontal gyrus					

GRF correction, voxel level: $p < 0.001$, cluster level: $p < 0.05$

Abbreviations: ASD, autism spectrum disorder; NVD, normal serum 25(OH)D; VDI, insufficient serum 25(OH)D; VDD, deficient serum 25(OH)D; MNI, Montreal Neurological Institute; ReHo, regional homogeneity

speculation. The precuneus, a part of the default mode network (DMN), plays a role in self-referential processing, introspection, and social cognition [44, 45]. Aberrant DMN functioning has been consistently reported in individuals with ASD and has been linked to core symptoms, including social and communication deficits [46–49]. Additionally, a study examining vitamin D levels and the risk of Parkinson's disease found that lower serum 25(OH)D levels affected spontaneous neuronal activity in the DMN in patients with Parkinson's disease [31]. The middle cingulate gyrus and superior frontal gyrus are involved in various cognitive and emotional processes, including social cognition, which is often impaired in individuals with ASD. The middle cingulate gyrus, in particular, plays a crucial role in cognitive control, error detection, and emotional regulation [50]. Dysfunction in these regions can lead to difficulties in social interaction and communication, which are core symptoms of ASD. ReHo in the right middle cingulate gyrus was negatively correlated with relating scores in patients with deficient and insufficient serum 25(OH)D levels. A previous study revealed that vitamin D insufficiency was associated with a thinner cingulate cortex in a sample of older adults [51].

In children with severe ASD, we observed that ReHo increased in the right middle temporal gyrus and right insula in the VDI group compared with the NVD group, and increased in the right superior frontal gyrus in the VDD group compared with the VDI group. The right middle temporal gyrus is closely associated with functions such as language comprehension, social cognition, and auditory processing, which are often impaired in individuals with ASD [52–54]. A study on Parkinson's disease found that vitamin D levels may modulate the spontaneous neural activity of the middle temporal

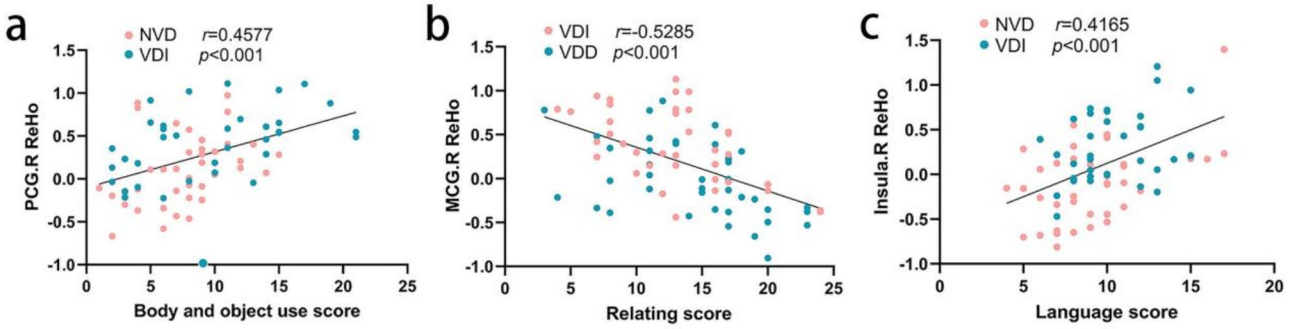

Fig. 3 Relationships between the ReHo values and psychopathological characteristics. **a**: Positive correlation between the ReHo values of the right postcentral gyrus and body and object use scores in the NVD and VDI groups of patients with mild ASD. **b**: Negative correlation between the ReHo values of the right middle cingulate gyrus and relating scores in the VDI and VDD groups of patients with mild ASD. **c**: Positive correlation between the ReHo values of the right insula and language scores in the NVD and VDI groups of severe ASD patients. Abbreviations: NVD, normal serum 25(OH)D; VDI, insufficient serum 25(OH)D; VDD, deficient serum 25(OH)D; PCG.R, right postcentral gyrus; MCG.R, Right middle cingulate gyrus

gyrus, thereby influencing cognitive function and the regulation of neural networks in patients [31]. On the other hand, the right insula is implicated in various functions, including interoceptive awareness, emotional regulation, sensory integration, and speech and language processes. Increased ReHo in this region could indicate heightened neural activity, potentially contributing to the sensory and emotional dysregulation commonly observed in ASD [55]. Jeremy et al. also reported abnormal insula function in individuals with ASD, demonstrating that the insula is overconnected to the retrosplenial cortex and increases internalization in patients with individuals with ASD [56]. Several clinical and animal studies have shown that vitamin D levels affect emotional regulation and sensory integration [57–61]. Furthermore, we observed that ReHo in the right insula was positively correlated with language scores. Research has shown that the insula plays a critical role in language production and speech articulation, supporting motor control of speech through its connection with Broca's area, while also coordinating higher-order cognitive functions related to language via its broader connections with other language-related regions [62–64]. Anderson et al. [65] also found that individuals with ASD exhibited decreased activity in the left posterior insula during auditory language tasks, suggesting that the insula plays a key role in auditory and language processing in ASD and may be linked to language impairments. The superior frontal gyrus plays a critical role in improving cognitive functions such as working memory, executive function, and social cognition, which are often impaired in individuals with ASD [66]. The observed increase in ReHo values in this region may indicate hyperactivity or compensatory mechanisms in response to deficient vitamin D levels. This hyperactivity could be a neural attempt to counterbalance the impaired functioning caused by the deficiency, but it might also lead to inefficient neural processing and connectivity.

Vitamin D not only plays a role in the functional activity of specific brain regions but also regulates broader neural networks that influence brain activity in individuals with ASD. Vitamin D deficiency is closely associated with various neurological diseases, cognitive decline, and emotional regulation disorders [67–69]. This association is not only due to its direct effects on neuronal function and neuroplasticity but also potentially through alterations in neural network connectivity, which can affect the functional integration between different brain regions [67, 70]. In our study, as vitamin D levels declined, we observed changes in ReHo values across multiple brain regions, suggesting that vitamin D deficiency affects not only local neural synchronization but also leads to broader neural network dysregulation. We hypothesize that vitamin D deficiency may impair neural synchronization locally and further disrupt overall network connectivity, thereby affecting cognitive functions, emotional regulation, and social interaction capabilities. Vitamin D's effects are not confined to specific brain regions but may also help coordinate and maintain communication between different brain areas, ensuring the stability and efficiency of neural networks. Based on these findings, future research should further explore the mechanisms by which vitamin D modulates neural network function in ASD, particularly how vitamin D supplementation might alleviate these neural dysfunctions. This will provide deeper insights into the role of vitamin D in brain health and may offer new therapeutic targets and intervention strategies for treating ASD.

Vitamin D levels are influenced by multiple factors related to sex. First, sex hormones play an important role in vitamin D metabolism. Research indicates that estrogen can increase the production of 1,25(OH)2-vitamin D by regulating vitamin D metabolism, thus promoting calcium absorption [71]. This suggests that females may have higher vitamin D levels when estrogen levels are elevated. Additionally, females typically have a higher

proportion of subcutaneous fat, which can store more vitamin D, potentially affecting its availability in circulation [72]. In contrast, fluctuations in testosterone levels in males may influence the vitamin D metabolism process differently [73]. Furthermore, males are generally exposed to more outdoor activities and sunlight, which could lead to higher vitamin D synthesis [74, 75]. These sex differences may contribute to different patterns of brain network function, activation, and connectivity between males and females through their effects on vitamin D metabolism. As this study controlled for sex differences between groups, we did not specifically analyze the impact of sex on vitamin D levels and brain function connectivity. Future studies should further explore how sex influences the effect of vitamin D on brain function connectivity in children with ASD, to better understand this complex relationship.

Limitations

There are several limitations to this study. First, all patients were sedated before the MRI due to their young age. Second, this study analyzed the relationship between vitamin D and brain function in individuals with ASD through a cross-sectional design. Future prospective studies, such as comparisons before and after vitamin D treatment, are needed to confirm our findings. Third, although this study focused on preschool children, this developmental stage is characterized by rapid brain growth. Therefore, future research should refine age groups to further investigate the precise impact of vitamin D on cognitive function at each developmental stage.

Conclusion

In conclusion, our study demonstrated that ASD patients with lower serum 25(OH)D levels exhibit multiple brain functional abnormalities, with alterations in specific brain regions correlated with the severity of symptoms. This study highlights the potential role of vitamin D in modulating brain function in children with ASD. These findings improve our understanding of the potential mechanisms by which vitamin D may affect patients with ASD, providing a foundation for future research into its potential therapeutic applications.

Abbreviations

ASD	Autism spectrum disorder
25(OH)D	25-hydroxyvitamin D
ReHo	Regional homogeneity
CARS	Childhood Autism Rating Scale
ABC	Autism Behavior Checklist
VDR	Vitamin D receptor
rs-fMRI	Resting-state functional magnetic resonance imaging
BOLD	Blood oxygen level dependent
TD	Typically developing
NVD	Normal serum 25(OH)D levels
VDI	Insufficient serum 25(OH)D levels
VDD	Deficient serum 25(OH)D levels
GRF	Gaussian random-field
DPARSF	A Data Processing Assistant for Resting-State fMRI Advanced Edition
MNI	Montreal Neurological Institute
DARTEL	Diffeomorphic Anatomical Registration Through Exponentiated Lie
KCC	Kendall's coefficient of concordance
DMN	Default mode network
IQR	Interquartile range
SD	Standard deviation

Author contributions

PT and DL was designed this study. PT and XZ conducted analyses and drafted the manuscript. ZL and BB contributed to processing of the data. FJ and DL revised the manuscript draft. LD, YJ, XL and TZ assisted in the acquisition and interpretation of the data. All authors approve the publication of the manuscript.

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Data availability

The datasets generated and/or analysed during the current study are not publicly available due to their containing information that could compromise the privacy of research participants, but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

We obtained informed consent from the parents or caregivers of the children who participated. This study was carried out in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of the First Hospital of Jilin University (23K195-002).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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