REGULATION OF BRAIN NETWORKS BY LEVETIRACETAM AND OXCARBAZEPINE IN CHILDREN WITH BENIGN CHILDHOOD SELF-LIMITED EPILEPSY WITH CENTROTEMPORAL SPIKES (SELECTS)

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ABSTRACT

Objective: *This study aimed to investigate the effects of levetiracetam (LEV) and oxcarbazepine (OXC) on structural brain networks and cognitive function in children with Self-Limited Epilepsy with Centrotemporal Spikes (SeLECTS) .*

Methods: *We recruited 21 children who were newly diagnosed with SeLECTS and divided them into LEV (n=10) and OXC groups (n=11). We obtained 3.0 T high-resolution T1-weighted magnetic resonance imaging (3D-T1 MRI) and neuropsychological assessment data before and 12 months after medication. The statistical parameter map data package was used to preprocess the magnetic resonance images. Changes in cerebral gray matter volume after treatment were compared within and between groups with voxel-based morphological analyses, and correlations between cerebral gray matter volume changes and cumulative doses of the drugs were analyzed.*

Results: *After treatment, the gray matter volume in the left putamen, left middle temporal gyrus, and left auxiliary motor area decreased significantly in the LEV group, while the gray matter volume in the left putamen, right cerebellum, and left postcentral gyrus increased significantly in the OXC group. The increased gray matter volumes in the right cerebellum and left middle occipital gyrus were significantly negatively correlated with the cumulative dose of OXC (r=-0.64, P =0.034; and r=-0.739, P=0.009, respectively). Neuropsychological evaluation showed that verbal, performance, and full-scale intelligence quotients in both groups increased after treatment, and the increase was statistically significant in the LEV group, but not in the OXC group.*

Conclusion: *Both OXC and LEV can regulate the brain regions affected in SeLECTS, but their action sites are different. LEV can significantly improve the brain structural network of children withSeLECTS , while some brain regions of children who are taking OXC may continue to suffer damage, as suggested by the increased gray matter volumes in those regions after OXC treatment. LEV can partly improve the cognitive function of children. The volume increase of the right cerebellum and left occipital gyrus gray matter was negatively correlated with the cumulative use of OXC, suggesting that OXC can improve the damage to brain structure in children with SeLECTS).*

Keywords: *Self-limited epilepsy with centrotemporal spikes (SeLECTS), levetiracetam, oxcarbazepine, voxel.*

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Introduction

Self-Limited Epilepsy with Centrotemporal Spikes (SeLECTS) is also known as benign lateral fissure epilepsy. It is a common disease of the pediatric nervous system, accounting for about 15-24% of epilepsy cases in children. The onset of the disease is often at the age of 3-13 years, peaking at 9-10 years. The symptoms mainly occur during sleep, often presenting as sudden, short, unilateral facial or oral motor seizures, accompanied by somatosensory symptoms(1). The development of the affected child is normal, and no abnormality is found on routine imaging examinations. Electroencephalogram (EEG) shows high-amplitude spikes and slow waves in the central temporal region, with normal background activity(2). The frequency of seizures in SeLECTS often decreases with age, and the disease disappears at puberty. Therefore, many scholars advocate that children with SeLECTS should not be treated with drugs. However, recent studies have shown that children with SeLECTS have language and cognitive impairment, and their early treatment is being paid more attention to[3]. At present, the primary choice of drugs for SeLECTS in China is oxcarbazepine (OXC), and the first-line drugs include levetiracetam (LEV). OXC is a ketone structural of carbamazepine (CBZ). It is mainly used in monotherapy or additive therapy for partial seizures in adults and children. It has the advantages of a quick effect, wide safety margin, and good tolerance. It has no significant effect on cognitive function[4].

LEV is a pyrrolidone subordinate, which is broadly utilized in the treatment of partial seizures in adults and children. It has the advantages of a simple assimilation, good tolerance, and high bioavailability[5]. LEV can cause a temporary and reversible decrease in white matter volume in the right posterior thalamic tubercle, occipital lobe, and parietal lobe of rhesus monkeys, suggesting that it alters the structural network of the brain[6]. At present, there is a lack of research on the effect of OXC on the structural network of the brain in children with SeLECTS, and studies on the effect of LEV on SeLECTS are also limited to horizontal comparisons. Longitudinal follow-up is necessary for observing the regulatory mechanism of these two new antiepileptic drugs (AEDs) on the structural network of the brain in SeLECTS) .

Voxel-based morphological analysis (voxel-based morphometry, VBM) is a novel automatic image analysis technique. By measuring the volume and density of brain tissue, the tissue characteristics and differences in local gray and white matter can be assessed, which can then be used to evaluate the fine structure of brain tissue. VBM has the advantages of being objective, comprehensive, repeatable, and unbiased[7]. In order to carry out accurate statistical analysis, we used the optimized VBM method to standardize the space on the gray and white matter template. The comparative statistical data obtained by this method are all from the gray or white matter, are not mixed with data for other non-gray matter components, and are not affected by other regions of the brain. Therefore, this method is objective and accurate. We have previously used VBM to study the differences in brain structural networks between children with SeLECTS and healthy children[8].

In the present study, we used VBM to explore the changes in the brain structure of children with SeLECTS before and after treatment with new AEDs-in this case, LEV or OXC monotherapy.

Materials and methods

Study design

This was an open, prospective, and comparative study that assessed the changes in the brain structural network of children newly diagnosed with SeLECTS, who were treated with LEV and OXC monotherapy.

Clinical data

Study subjects

The case group consisted of 26 children with SeLECTS who were on their first visit or had not been provided treatment at the Department of Neurology and Pediatrics of the Affiliated Hospital of North Sichuan Medical College. The subjects were recruited from December 2013 to December 2017 (see Table 1 for demographic and clinical details), and they were jointly diagnosed by two pediatric neurologists, based on clinical manifestations, EEG features, and computed tomography and/or magnetic resonance imaging (MRI) findings.

Inclusion criteria:

- We included patients who met the diagnostic criteria for SeLECTS based on the 1989 diagnostic classification criteria for epilepsy and epilepsy syndrome;
- Did not take any AED before visiting the doctor;
- Were not concurrently suffering from other neuropsychological diseases, such as attention deficit hyperactivity disorder;
- Were able to cooperate with independent completion of neuropsychological evaluation and MRI data acquisition;
- Had no seizures during the MRI scan and one day before;
- Were right-handed based on the result of Chinese handedness rating scale and spoke Chinese as their first language;
- Required drug treatment and had no contraindications to LEV or OXC.

Exclusion criteria:

- We excluded patients who showed epileptic discharge in the central temporal region on EEG but had no SeLECTS clinically;
- Had a history of abnormal brain development, mental illness, or other serious medical diseases;
- Were less than 6 years old (it was difficult for them to cooperate with neuropsychological evaluation or MRI data acquisition);
- Had contraindications to MRI, such as having

prosthesis implantation or metal foreign bodies;

• Received glucocorticoid or other immune drugs 6 months before OXC or LEV treatment;

• Switched to or combined other antiepileptic drugs with OXC or LEV during treatment.

Ethics

This study was approved by the Ethics Committee of the Affiliated Hospital of North Sichuan Medical University (2022ER259-1) and was conducted in accordance with the Declaration of Helsinki.

The family members or guardians of all the subjects in this study signed the informed consent form and were able to cooperate with the researchers till the completion of this study.

Research methods

Neuropsychological assessment

The components of the neuropsychological assessment included general knowledge, vocabulary, arithmetic, classification, understanding, mapping, arrangement, jigsaw puzzle, building blocks, and coding. After the assessment, we obtained the full-scale intelligence quotient (IQ)/total IQ (FSIQ), verbal IQ (VIQ), and operational/performance IQ (PIQ). All subjects were assessed in a quiet and comfortable environment, at about 9:00 am.

After completing the test, they were treated with OXC or LEV, and the above neuropsychological data were collected again 12 months later.

Image data acquisition of brain structural network

Routine head MRI (conventional T1-weighted imaging, T2-weighted imaging, T2/FLAIR-weighted imaging, etc.) and 3D-T1 data were collected before and 12 months after drug administration in all subjects. All magnetic resonance images were collected by the same technician, who was blinded to the patient's clinical condition, using a 32-channel head coil 3.0 Tesla superconducting MRI system (Discovery MR750, General Electric, Boston, MA, USA). This study was carried out in the Magnetic Resonance Room of the Affiliated Hospital of North Sichuan Medical College.

The research team was composed of magnetic resonance technicians, imaging diagnostics experts, and neurologists. The following 3D-T1 data parameters were used: fast scrambling gradient echo sequence, repetition time= 6.008 ms, echo time= 1.984 ms, flip angle = 9, matrix = 256 × 256, field of view = 25.6 cm × 25.6 cm, slice thickness = 1 mm, and spacing (gap) = 0 mm.

Main instruments and drugs

We used a 3.0 Tesla superconducting MRI system (GE Discovery MR750), 32-channel head coil (General Electric), LEV (Belgian UCB, 250 mg/, batch number H20060377), and OXC (Swiss Novartis, 150 mg/, batch number S0028A).

Drug intervention

The patients were treated with LEV or OXC monotherapy. The initial dose of LEV was 10 mg/kg/day, twice a day. The dose was gradually adjusted according to the curative effect observed (increased or decreased by 10 mg/kg every 2 weeks), and the final dose was maintained at 10-30 mg/kg/day.

The initial dose of OXC was 8-10 mg/kg/day, twice a day. The dose was gradually adjusted according to the curative effect observed (increased or decreased by 10 mg/kg every 2 weeks), and the final dose was maintained at 10-46 mg/kg/day.

Data processing and analysis

General data

We used Statistical Package for the Social Sciences version 23.0 for data analysis.

General clinical data in the two groups were analyzed with the chi square test or double sample t-test as appropriate.

Neuropsychological data analysis

Neuropsychological data were expressed as mean ± standard deviation and analyzed with repeated measures analysis of variance. A two sample t-test was used for inter-group difference analysis, and a paired t-test was used for intra-group difference analysis.

VBM

Before VBM analysis, all 3D-T1 images were preprocessed with statistical parametric mapping (SPM8).

The preprocessing mainly included the following:

• Head movement correction: since small head movement in the experiment could cause artifacts and affect the subsequent statistical analysis, we invited experienced imaging experts to check the

T1 images to assess whether the edge of each image was smooth or the image was distorted as a whole, and to exclude images with obvious deformation and distortion.

- Spatial standardization: a non-linear algorithm was used to standardize the individual space, and the resulting average-sized image was further standardized in the standard template space through affine spatial standardization.
- Image segmentation: the registered image was segmented into white matter, gray matter, and cerebrospinal fluid, using unified standard segmentation procedure.
- Spatial smoothing: images were smoothed using SPM, and isotropic Gaussian kernel (8 mm HM) was used to smooth segmented gray matter images.

After processing, 3D-T1 images from two SeLECTS patients were discarded due to excessive head movement. In SPM8, the volumes of cerebral gray matter in the two groups before and after treatment were compared by repeated measures analysis of variance. The significance level of population difference was set at P<0.05 (uncorrected), and then the brain regions with significant differences were posterior tested with the double sample t-test and paired t-test.

The gray matter volumes of brain areas with significant differences between the two groups were analyzed and correlated with the cumulative doses of the drugs and neuropsychological evaluation data (FSIQ, VIQ, and PIQ).

Results

General data

Among the 26 children, two were excluded due to excessive head movement during data acquisition, one was lost to follow-up, and two withdrew due to switching to other medications.

Finally, 21 subjects completed the experiment, including 10 in the LEV group and 11 in the OXC group. There were 14 males (53.85%) and 12 females (46.15%). The seizure frequency ranged from 2-11 times/year: 2 times/year in three cases, 3-4 times/year in 13 cases, and more than five times/year in five cases. The age range was 6.12-11.92 years.

The sex and average age of patients in the LEV and OXC groups were compared with the chi-square test and two sample t-test, respectively, and there was no statistically significant difference (all P>0.05, see Table 1).

	LEV group	OXC group	*P-value*
Age at onset (years)	8.28±1.60	8.14±2.04	0.899[a]
Disease course (years)	1.04±0.49	1.32±0.45	0.186[a]
Age (years)	8.99±1.67	9.46±2.35	0.671[a]
Sex (male/female), n	10 (5/5)	11 (7/4)	0.513[b]

Table 1: Demographic and clinical data.
Data are presented as mean ± standard deviation. [a] t value of double samples; [b] chi-square value. LEV, levetiracetam; OXC, oxcarbazepine.

Neuropsychological evaluation

After administration of medication, both groups showed increased VIQ, PIQ, and FSIQ scores, but there was no significant change in the scores of the OXC group after treatment, while the post-medication increase in VIQ, PIQ, and FSIQ scores in the LEV group was statistically significant (P<0.05, Table 2).

	LEV group		OXC group		*P-value*	Posterior (paired t-test)		Posterior (two-sample t-test)	
	Baseline	12 months	Baseline	12 months	=0.000	*P-value* (OXC group)	*P-value* (LEV group)	*P-value* baseline	*P-value* (12 months)
VIC	81.09± 5.52	78.16± 2.86	81.54± 5.06	81.83± 3.25	=0.000	0.341	<0.001	0.249	0.862
PIQ	90.27± 5.93	89.90± 5.67	89.81± 6.71	94.16± 5.19	=0.000	0.320	<0.001	0.884	0.369
FSIQ	83.63± 4.10	82.50± 2.50	84.27± 3.23	86.33± 2.16	=0.000	0.532	<0.001	0.549	0.347

Table 2: Comparison of WSCI results between the two groups before and after treatment.
Data are presented as mean ± standard deviation. VIQ, verbal intelligence quotient; PIQ, performance intelligence quotient; FSIQ, full-scale intelligence quotient; LEV, levetiracetam; OXC, oxcarbazepine; WSCI, Wechsler intelligence scale for children.

VBM

Compared with that before treatment, gray matter volume increased in three brain regions in the OXC group, and the difference was statistically significant (P<0.05, Table 3, Figure 1).

Brain area		MNI coordinates			*F*	Voxel
		X	Y	Z		
Right cerebellum	-	30	-36	-36	11.14	22
Left middle temporal gyrus	BA 21	-60	-33	-9	19.60	63
Left middle occipital gyrus	BA 19	-30	-78	9	9.41	41
Left putamen	BA 49	-27	-6	9	10.11	65
Left posterior central gyrus	BA 4	-33	-24	48	8.93	20
Left auxiliary motor area	BA 6	-9	-6	78	9.56	93

Table 3: Areas of the brain with significant changes after treatment.
BA, Brodmann area ; MNI, Montreal Neurology Institute.

Figure 1 shows that the increased gray matter volume was noted in the left putamen, right cerebellum, and left retrocentral gyrus, while the gray matter volume of the left putamen, left middle temporal gyrus, and left auxiliary motor area in the LEV group decreased, and the difference was statistically significant (P<0.05, Table 3, Figure 1).

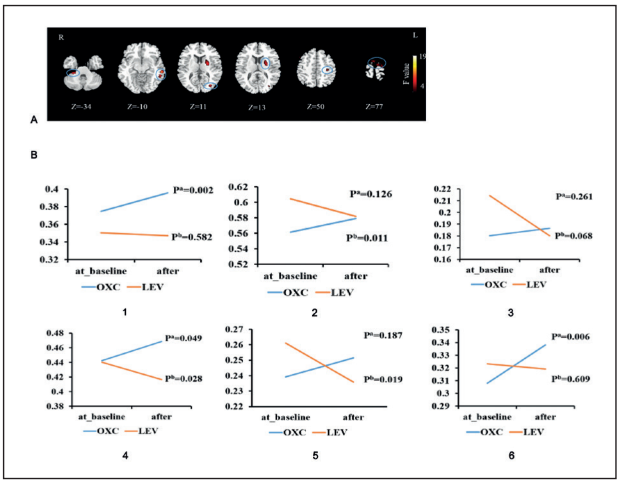

Figure 1: Changes in gray matter volume in patients with BECTS who were treated with OXC or LEV. A: The results of Avar 2×2 repeated measurement analysis of variance. B: Posterior test results.

[a] *results of the paired t-test in the OXC group;* [b] *results of the paired t-test in the LEV group. 1: right cerebellum; 2: left middle temporal gyrus; 3: left middle occipital gyrus; 4: left putamen; 5: left auxiliary motor area; 6: left posterior central gyrus BECTS, benign childhood epilepsy with centrotemporal spikes; LEV, levetiracetam; OXC, oxcarbazepine.*

Correlation between brain structural network and cumulative doses of OXC and LEV

The increases in gray matter volume in the right cerebellum and left occipital gyrus were negatively correlated with the cumulative dose of OXC (r = 0.64 and r= 0.739, respectively; Figure 2). The average cumulative dose in the LEV group was 345.00±73.04 g, and no significant correlation was found between the changes in gray matter volume and clinical factors (cumulative dose of LEV, age, course of disease, and neuropsychological data).

Discussion

Self-Limited Epilepsy with Centrotemporal Spikes (SeLECTS) is the most common kind of epileptic syndrome in children. It could be a combination of maladies characterized by anomalous synchronous releases of brain neurons due to an assortment of causes, with paroxysmal, temporal, monotonous, and stereotyped characteristics. This study explored the changes in the brain structure of children with SeLECTS before and after treatment with LEV or OXC.

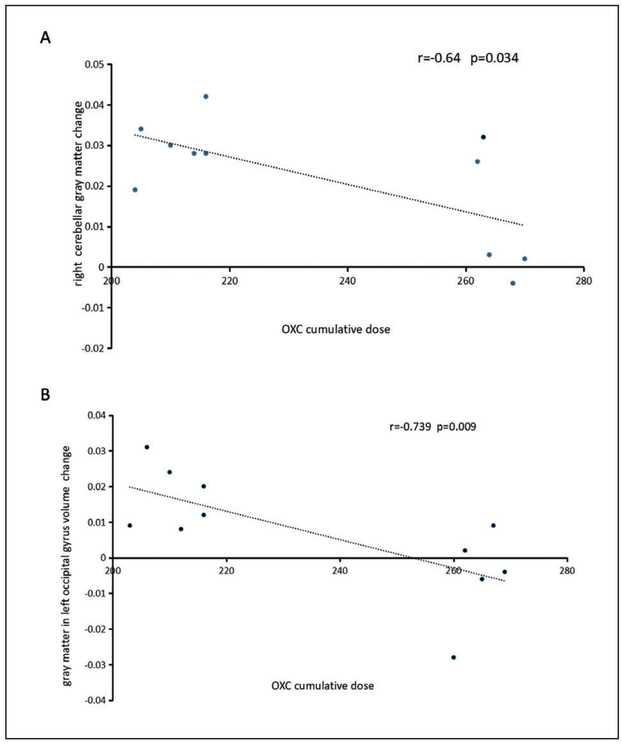

Figure 2: A: Correlation of right cerebellar gray matter volume with oxcarbazepine dose
After controlling for the influence of age and sex, the increase in right cerebellar gray matter volume was significantly negatively correlated with the dose of oxcarbazepine (OXC). B: Correlation of gray matter volume in the left occipital gyrus with oxcarbazepine dose After controlling for the influence of age and sex, the increased gray matter volume in the left occipital gyrus was significantly negatively correlated with the dose of oxcarbazepine (OXC).

It used to be difficult to discover anomalous brain structure with ordinary imaging modalities, but with the application of imaging techniques such as VBM, increasing proofs have appeared that the brain structure is harmed in SeLECTS. Children with SeLECTS have learning difficulties, short-term memory loss, and short attention span. The increase in gray matter volume in motor- and language-related areas may be the evidence of progressive damage to the brain structure. The results of this study showed that after LEV treatment, the volume of gray matter in motor- and language-related areas of the brain decreased significantly, and language and other cognitive functions improved, suggesting that LEV can correct the abnormality of brain structure and network in children with epilepsy. Although epilepsy was effectively controlled in the OXC group, there was still an increase in gray matter volume, suggesting progressive subclinical damage, which may be caused by continued epileptic discharge. These findings suggest the importance of early pharmacologic intervention.

In a previous study, we found an increase in gray matter volume in the right inferior temporal gyrus and right insular/tegmental part of the forebrain in children with SeLECTS[8]. It is suggested that changes in cognitive function in children may be compensated by non-dominant cerebral hemispheres. Previous studies have however not found changes in gray matter volume in language-related areas of the dominant hemispheres, which may be because those studies included children who were on medication. The traditional view is that the language function of healthy right-handed people is mainly controlled by the left hemisphere. In this study, we found reduced gray matter volume in the left middle temporal gyrus after LEV administration, and the results of neuropsychological evaluation also showed that VIQ improved after treatment. Therefore, we speculate that the reduced gray matter volume in the left middle temporal gyrus in children with SeLECTS may be related to the therapeutic effect of LEV on the brain network of language-related structures. Although, in the correlation analysis, we did not find any correlation between the reduced gray matter volume in the left middle temporal gyrus and the cumulative dose of LEV, probably because the sample size was not large enough; the possibility is worth further discussion.

Our study found that the gray matter volume in the left putamen, left middle temporal gyrus, and left auxiliary motor area decreased significantly in the LEV group after treatment, while the gray matter volume in the left putamen, right cerebellum, and left postcentral gyrus increased significantly in the OXC group after treatment. These findings preliminarily show that different novel AEDs have different regulatory actions on the brain structural network in children with SeLECTS. FSIQ, VIQ, and PIQ in the LEV group significantly increased after treatment, indicating that LEV can improve the cognitive function of patients, but this phenomenon was not observed in the OXC group. However, it is still necessary to expand the sample size, refine the evaluation methods, and adopt a multicenter comparative approach to clarify the potential pathophysiological mechanism of OXC. A previous study found an increase in the gray matter volume in the left putamen of newly diagnosed children with SeLECTS[10], suggesting that the areas related to brain information processing and task execution were damaged. It is generally believed that during childhood and puberty, the development of the putamen will decline linearly with age[11]. In the current study, children with SeLECTS showed a decrease in the gray matter volume in the left putamen after LEV administration, which was consistent with the previously observed results and also with the characteristics of normal brain development in children. Therefore, we speculated that LEV corrected the network related to information processing and task execution. Previous studies have found that LEV has a corrective effect on enlarged bilateral paracentral lobules and bilateral auxiliary motor areas in children with SeLECTS[12], but this phenomenon was not observed in the present study. Children with SeLECTS often have co-existing cognitive disorders such as language impairment, attention deficit, and learning difficulties[13].

Brain structure shows increased gray matter volume in the right inferior temporal gyrus, right anterior insular lobe/tegmental area, left superior frontal gyrus, and right middle frontal gyrus, which are related to cognition and language. LEV had no adverse effect on children's cognitive function in this study; rather, it improved speech fluency and attention, and has the potential to improve 'oral expression, memory, and interpersonal skills.

This study found that the gray matter volume in the left middle temporal gyrus of children with SeLECTS was significantly reduced after LEV administration, and that the language function of healthy right-handed children was mainly regulated by the left cerebral hemisphere. The results further support the fact that LEV can correct disorder of the language-related brain structural network in children with SeLECTS. Some scholars have found a correlation between LEV dose and brain functional network signals in patients with drug-resistant temporal lobe epilepsy[14], but in this study, no significant correlation was found between LEV dose and the brain structural network. Further research on this is warranted. In the OXC group, we observed a significant increase in gray matter volume in the left putamen. Structural abnormalities of the left putamen in children with SeLECTS are associated with interictal epileptic discharges, and chronic epileptic activity may affect their normal developmental trajectory, resulting in increased gray matter volume in the left putamen.

In this study, the subjects showed increased gray matter volume in the putamen after OXC treatment. This may be because OXC does not completely correct disorders of the brain structural network of children with chronic epileptic activity, or because the mechanisms of action of OXC and LEV are different, and they have unique regulatory characteristics. This study also found that the gray matter volume in the right cerebellum, which is involved in coordinated movement, increased after OXC treatment, and the cumulative dose of OXC was negatively correlated with increased right cerebellar gray matter volume of children with SeLECTS.

The lower the dosage of OXC, the greater the increase in right cerebellar gray matter volume, suggesting that OXC can correct the brain structure of children with SeLECTS. The structure of CBZ is similar to that of OXC. Studies have shown that the brain functional network of patients taking CBZ has decreased signal activity in the left inferior frontal gyrus, and that their frontal lobe-related functional activation network is dysregulated. This suggests that OXC, which has a similar mechanism of action, may regulate language-related networks (e.g., in the frontal lobes). In our study, both LEV and OXC had obvious regulatory effect on the left putamen in children with SeLECTS, but the results were different: the gray matter volume of the left putamen decreased in the LEV group, while it increased in the OXC group, probably due to the different mechanisms of action of the drugs.

There are also differences in the structural regulation targets of the two drugs in the brain. LEV mainly acts on the left putamen, left middle temporal gyrus, and left auxiliary motor area, while OXC mainly acts on the left putamen, right cerebellum, and left postcentral gyrus. Accordingly, LEV mainly reduced the structural volume of its corresponding brain regions, while OXC mainly increased the structural volume of its corresponding brain regions. Our findings may therefore delineate that different AEDs exhibit different patterns of motor- and language-related structural network regulation in SeLECTS patients.

This study has the following limitations:

• The sample size is small, and some of the results are not comparable, which limits the generalization of the research results to a certain extent.

• In the process of imaging data collection, although no clinical seizures were observed, the interference of subclinical epileptic discharge in the scanning process was not ruled out. In future research, we will further expand the sample size, utilize synchronous EEG-fMRI technology, monitor the activity of brain neurons during resting-state scanning, and evaluate the relationship between subclinical epileptic discharges and changes in brain structure and function.

Conclusion

• Both OXC and LEV can regulate SeLECTS -related brain regions, but there are differences in their sites of action. LEV significantly improved the brain structural network of children with SeLECTS , while the gray matter volume of some brain regions still increased after treatment with OXC, suggesting that those brain regions may be continuously damaged.

• VIQ, PIQ, and FSIQ scores in the LEV group all improved after treatment, which suggests that LEV can partially improve the cognitive function of children with SeLECTS.

• Increased gray matter volumes in the right cerebellum and left middle occipital gyrus were negatively correlated with the cumulative dose of OXC, suggesting that OXC can improve brain structure.

Summary and prospect

In this study, neuropsychological evaluation methods and magnetic resonance structural imaging were combined to verify that LEV has no adverse cognitive effect on children with SeLECTS, and LEV and OXC have different regulation points in the brain structural network.

These findings produce behavioral and imaging proof for the treatment of SeLECTS. They also suggest that language and executive dysfunctions in children with SeLECTS are related to the changes in motor- and language-related structural networks of the brain, caused by chronic epileptic activity and that LEV may correct these brain structural disorders.

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