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ORIGINAL PAPER

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Regional cerebral perfusion abnormalities in developmental language disorder

Statistical parametric mapping analysis

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Abstract *Objective* A voxel based investigation of cerebral blood flow was conducted to identify brain functional differences during resting state between children with developmental language disorder (DLD) and normal controls. *Method* Using DSM-IV criteria, we selected 21 children with DLD. All children were examined by technetium-99m-HMPAO Brain SPECT. Using SPM analyses, we compared the SPECT images of children with DLD and those of 17 control subjects on a voxel by voxel basis using ANCOVA covarying for age. *Results* Reduced cerebral blood flow in the right putamen, the right inferior parietal cortex, and the left globus pallidus were found in children with DLD versus the controls. However, no area of increased cerebral blood flow was observed in children with DLD compared to the controls. *Conclusion* Though results should be interpreted cautiously, this study confirms the presence of functional defects in the basal ganglia and the inferior parietal lobe during the resting state of the brains of children with DLD. It also gives further evidence for functional deficits in basal ganglia as an important factor in the etiology of DLD.

Key words developmental language disorder · SPECT · statistical parametric mapping

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Introduction

Problems of language are one of the most common issues in children from three to sixteen years of age, regardless of diagnosis (Shapiro 1989). In the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), language problems are described as a communication disorder and further divided into various subtypes (American Psychiatric Association 1994). In the International Statistical Classification of Disease and Related Health Problems (ICD-10), language problems are classified as specific developmental disorders of speech and language. Developmental language disorder (DLD) in the DSM-IV classification system is also called developmental dysphasia, developmental aphasia, or specific language impairment. In children with DLD, their developmental level of language is substantially below their expected level from intelligence (American Psychiatric Association 1994).

In the neuroimaging studies of DLD, reported areas in which abnormalities have been found are inconsistent (Trauner et al. 2000; Preis et al. 2000). Besides decreased white matter volume and increased white matter volume, various kinds of abnormalities have been reported in the corpus callosum, the left planum temporale, and the inferior frontal gyrus (Jernigan et al. 1991; Plante et al. 1991; Filipek et al. 1992; Njiokiktjien et al. 1994; Woodhouse et al. 1996; Clark et al. 1998; Davidovitch et al. 2000; Herbert et al. 2003, 2004). In addition, children with DLD had loss of leftward asymmetry which was closely similar to those in autistic children (Herbert et al. 2005).

In functional neuroimaging studies, findings are even more inconsistent. During the resting state, hypoperfusion in the bilateral perisylvian area, the left parieto-temporal area, and the left temporo-frontal area have been found in previous SPECT studies with xenon-133 or technetium-99m-HMPAO (Lou et al. 1984, 1990; Denays et al. 1989). In a recent technetium-99m-HMPAO SPECT study, abnormalities in the subcortical regions

and the right parietal regions were also reported (Ors et al. 2005). In addition, a failure to activate the left hemisphere during the phonemic discrimination task as well as an activation in the right hemisphere during a passive listening task have been found (Tzourio et al. 1992; Bernal and Altman 2003). However, most functional studies have been based on the region of interest method, which has limitations such as higher observer dependence, low reliability and limited examinations of other brain regions. In addition, regions of interest have been invariably large and have involved heterogenous subregions within brain structures (Busatto et al. 2000). Most subjects in past functional imaging studies in children with DLD were school-aged children and heterogenous (i. e., subjects were included with other comorbid psychiatric conditions, such as attention-deficit/hyperactivity disorder), which makes it difficult to distinguish functional deficits due to DLD during earlier stages of language development.

This is the first study to evaluate differences in brain perfusion during the resting state between children with DLD and control children using automatic voxel based statistical parametric mapping (SPM). Like DLD, in the absence of established hypothetical regional abnormalities, the SPM method is more useful than the ROI method for study purposes. In this study we measured resting rCBF by SPECT in preschool children, and compared their results with those of control subjects.

Methods

Subjects

Characteristics of the patients

Before study commencement, its nature and purpose were fully explained to children and their parents and written consent was obtained from each parent. All procedures in this study were performed according to the Procedure Guideline of Society of Nuclear Medicine Brain Imaging Council (Juni et al. 1998). The Ethics Committee of the Department of Nuclear Medicine and Neuropsychiatry at Seoul National University approved the study protocol. In the committee, any potential benefits and/or risks that were associated with procedures in this study were discussed. It was concluded that, although the risk of procedures including radiation exposure might be greater than minimal in children, it would be a minor increase and that results of this study would contribute much to our understanding of the subjects' disorders.

A total of 21 right-handed children with DLD including 14 boys and 7 girls (mean age: 4.2 ± 0.8 years) participated in this study. All children with DLD were clinically diagnosed according to the DSM-IV (American Psychiatric Association 1994). Children with delayed speech were included if no evidence of any significant developmental delay other than in a language domain existed and at least two certified child psychiatrists and one child linguist agreed upon a diagnosis of DLD. If the clinical diagnosis was DLD, but other diagnoses including mental retardation or pervasive developmental disorder could not be excluded after evaluating developmental history and conducting a clinical interview, we assessed their intellectual and developmental abilities using the Korean version of the Wechsler Intelligence Scale for Children-Revised (Wechsler 1974), the Vineland Social Maturity Scale (Doll 1965), the Psycho-Educational Profile (Schopler and Reichler 1979), and the Child Autism Rating Scale (Schopler et al. 1980) according to age and clinical manifestations. If significant deficits in nonverbal intelligence were suggested or if the total score of the Child Autism Rating Scale was in the autistic range, the case was excluded. All subjects had been living in ordinary family environments and were free from any general medical conditions. This was confirmed by medical and neurological examinations and by laboratory tests. No subject had a history of head trauma or evidence of a hearing difficulty.

The language levels of our DLD subjects were assessed using the Korean version of the Evaluation of Acquired Skills in Communication-Revised (EASIC-R) (Riley 1991), the Minnesota Child Development Inventory (CDI) (Ireton and Thwing 1976), the Receptive-Expressive Emergent Language Test (REEL) (Bzoch and League 1971), and the Preschool Language Scale (PLS) (Zimmerman and Steiner 1979). Linguists used combinations of these tests according to developmental level of language and finally estimated the expressive and receptive language level ranges of all subjects. The clinical characteristics of children with DLD are presented in Table 1. All children had mixed receptive-expressive impairments.

Controls and assessment

Control subjects were collected retrospectively from among children who had undergone brain SPECT studies during the past 3 years at our institute. They were mainly recruited from the Department of Pediatrics. However, all had been referred to the Division of Child and Adolescent Psychiatry because no specific organic causes could be found to explain their symptoms after P/E and brain imaging (including MRI, SPECT, EEG). All were evaluated by the psychological assessment and psychiatric interview. At which time they all were screened using CBCL. No definite meaningful T-score in the CBCL was found. Finally, 17 age-matched subjects who met the following criteria were selected as controls: (1) the subject had no abnormal findings by EEG, MRI, or brain SPECT by expert visual decision; (2) the subject had already been psychologically assessed and showed no evidence of any other psychiatric problem by psychiatric interview or by clinical scales; and (3) the subject had no medical history of a loss of consciousness, no neurological illness, and no serious behavioral problems. Most of the normal controls had a diagnosis of tension headache. Among the 17 controls, the primary diagnosis of 11 children was the somatoform disorder, NOS (their chief complaint was tension headache related to tension or stress especially during academic examinations). Five children had no psychiatric diagnoses (they required an examination after mild physical injury). One suffered from adjustment disorder with mild depressive symptoms (she also complained of frequent headaches and received play therapy). The characteristics of control subjects are presented in Table 1.

Image processing and analysis by statistical parametric mapping

SPECT imaging protocol

All subjects lay in the supine position, with eyes closed, in a quiet room with dimmed lights. In uncooperative cases or for those unable to keep the head still, we used oral chloral hydrate (50 mg/kg, not exceeding a total of 1000 mg per day) for sedation. Based on body weight of subjects (7.4–11.1 MBq/kg), technetium-99m-HMPAO was administered. SPECT images were acquired using a triple head gamma camera (Prism 3000; Picker International, Cleveland, OH) with a low-energy, high-resolution parallel hole collimator. The energy window was set at 140 keV with a 15% width. One hundred and twenty frames were acquired, in the step-and-shoot mode, with an acquisition time of 20 seconds per frame. Frames were 128×128 pixels in size, transaxial images were reconstructed as 64×64 matrixes and slice thickness of 1.67 mm, which were filtered with a Metz filter ($x = 1.5 \sim 2.0$); all images were corrected for attenuation using Chang's method (Chang 1978). Finally, 40–50 images from the top of the cerebral cortex to the bottom of the cerebellum perpendicular to the orbito-meatal line were reconstructed.

Statistical parametric mapping analysis

Statistical parametric mapping (SPM) (Talairach and Tournoux 1988; Friston et al. 1989, 1990, 1991, 1995a, 1995b) was used to determine quantitative differences between technetium-99m-HMPAO SPECT

Table 1 Demographic variables in patients

Variables/group	DLD (n = 21)	Control (n = 17)
AGE[a]		
Mean (S.D.)	4.2 (0.8)	11.0 (1.9)
Gender	Boys (14):Girls (7)	Boys (13):Girls (4)
Language Level		NC
Expressive		
Mean (S.D.)	2.2 (1.0)	
Receptive		
Mean (S.D.)	2.1 (1.1)	
KWISC	NC	
Mean (S.D.)		101.3 (11.2)
Range		100–121

[a] statistically significant ($p < 0.001$)

images of children with DLD and those of control subjects. SPM has been used in analyses of functional neuroimaging data of children with childhood psychiatric disorders including major depressive disorder and attention-deficit hyperactivity disorder, as well as those of adults (Bonte et al. 2001; Kim et al. 2002; Asahi et al. 2004; Shirao et al. 2005). Using SPM 99 (Statistical Parametric Mapping 99, Wellcome Department of Cognitive Neurology, London, UK) software, all images were spatially normalized onto the technetium-99m-HMPAO SPECT standard template provided with the SPM software to remove inter-subject anatomical variabilities (Friston et al. 1991, 1995a, 1995b). Affine transformation was performed to determine which 12 optimal parameters to use to register the brain on the template. Subtle differences between the transformed image and the template were removed by the nonlinear registration method using the weighted sum of the pre-defined smooth basis functions using a discrete cosine transformation. Spatially normalized images were smoothed by convolution using an isotropic Gaussian kernel with 16-mm FWHM. The aim of smoothing was to increase the signal-to-noise ratio and to account for variations in subtle anatomical structures. The count of each voxel was normalized versus the total brain count (proportional scaling in SPM) to remove global CBF differences between the individuals. After spatial and count normalization, significant differences between the SPECT images of children with DLD and control subjects were estimated at every voxel covarying their age using the ANCOVA statistical module in SPM 99. Differences between groups were initially detected using a voxel threshold probability of 0.001 and an extent threshold of 50 contiguous voxels. Moreover, because uncorrected results are prone to false-positives, we confirmed the differences, correcting for multiple voxel-wise comparison at a voxel threshold probability of 0.05.

Results

Regions of resting perfusion defect in children with DLD

As shown in Fig. 1 and Table 2, 5 voxel clusters were initially found to have significantly reduced HMPAO uptake in children with DLD, but 2 voxel clusters were regarded as a scalp artifact. The remaining areas were the right inferior parietal lobe (voxel numbers: 301, $Z = 5.00$, uncorrected $p < 0.001$), the right putamen (voxel numbers: 107, $Z = 5.23$, uncorrected $p < 0.001$), and the left globus pallidus (voxel numbers: 684, $Z = 4.24$, uncorrected $p < 0.001$) (Fig. 1, Table 2). After corrected for multiple comparison, significant differences remained in the right inferior parietal lobe (voxel numbers: 4, $Z = 5.00$, corrected $p < 0.05$) and right putamen (voxel

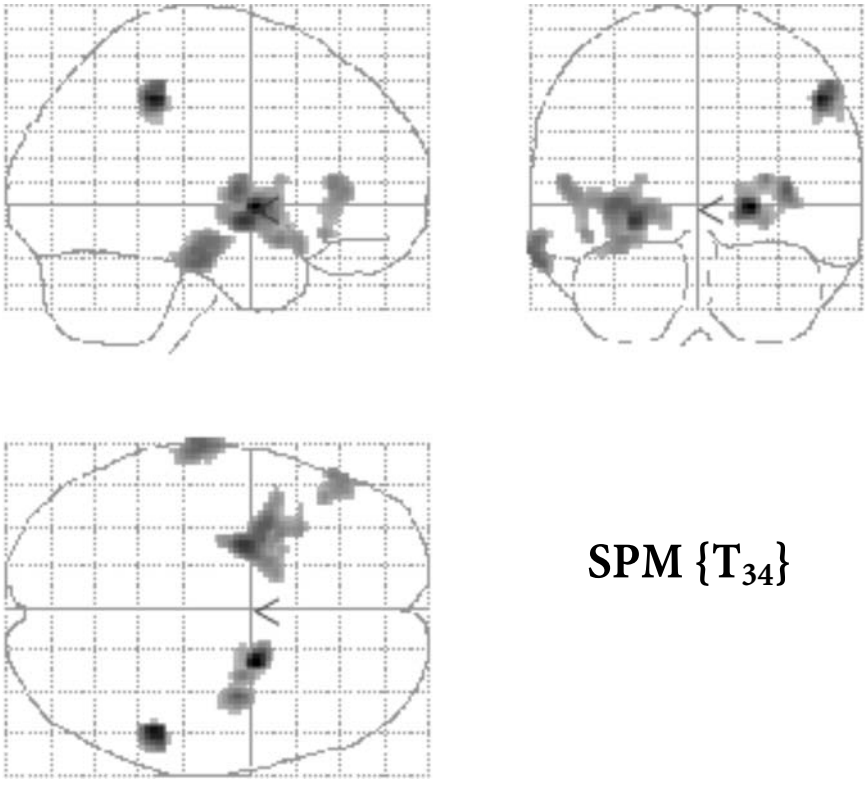

Fig. 1 Brain areas with significantly decreased perfusion in DLD patients compared to normal controls (threshold: P = 0.001, uncorrected). In this figure, three large clusters are shown: the right inferior parietal lobe, the right putamen, and the left globus pallidus

Table 2 Brain areas with significantly decreased perfusion in DLD patients compared to normal controls (threshold: P = 0.001, uncorrected)

Number of voxels	Brain regions included in cluster	Side	Coordinates (x, y, z)	Peak Z-value	P value (corrected)
301	Inferior parietal lobe	Right	50, –40, 44	5.00	< 0.001
107	Putamen	Right	22, 2, 0	5.23	< 0.001
684	Globus pallidus	Left	–34, 6, 0	4.24	< 0.001

numbers: 4, Z = 5.23, corrected p < 0.001), but not in the left globus pallidus (Fig. 2, Table 3).

Regions of resting perfusion overactivity in children with DLD

There were no significant increases in HMPAO uptake in children with DLD relative to control subjects.

Discussion

In the current study, we report decreased perfusion during the resting state in the right putamen, the left globus pallidus, and the right inferior paritetal lobe in children with DLD compared to control subjects. In addition, children with DLD had no areas of increased perfusion compared to control subjects. When the data were corrected for multiple comparisons, children with DLD had significantly decreased perfusion in the right putamen and the right inferior parietal lobe.

To the best of our knowledge, the current report is the first study evaluating perfusion differences between children with DLD and control subjects using SPM analyses. Prior neuroimaging studies in children with DLD have reported abnormalities in various areas. In structural neuroimaging studies, decreased whole brain volume (Preis et al. 2000; Davidovitch et al. 2000), increased white matter volume (Filipek et al. 1992; Woodhouse et al. 1996; Herbert et al. 2003, 2004), larger corpus callosum (Njiokiktjien et al. 1994), loss of normal asym-

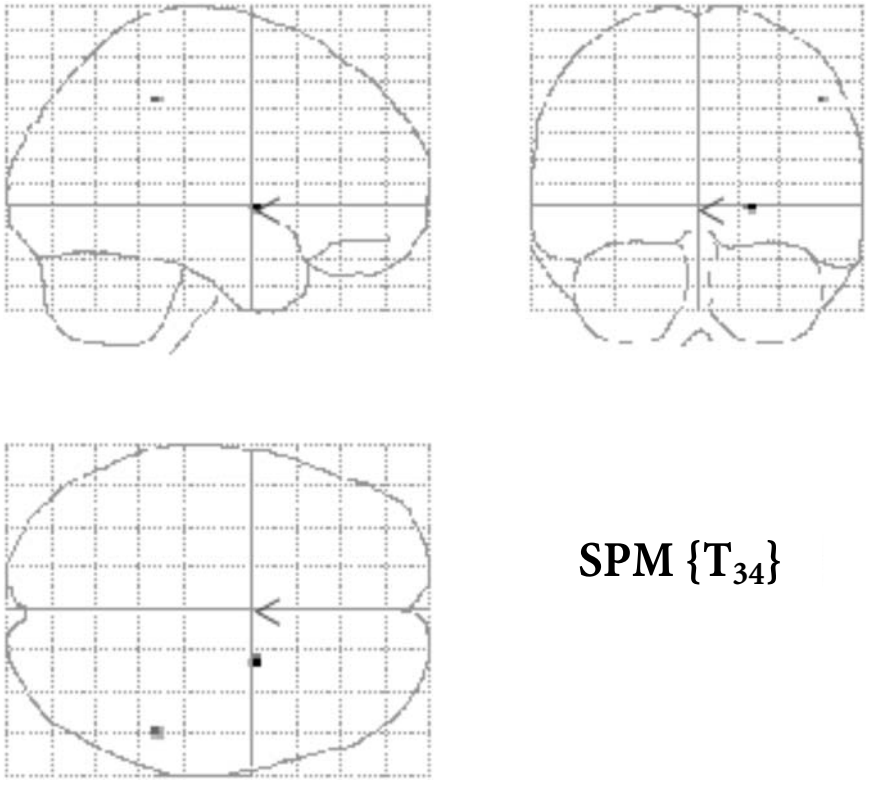

Fig. 2 Brain areas with significantly decreased perfusion in DLD patients compared to normal controls (threshold: P = 0.05, corrected). In this figure, two small clusters are shown: the right inferior parietal lobe and the right putamen

Table 3 Brain areas with significantly decreased perfusion in DLD patients compared to normal controls (threshold: P = 0.05, corrected)

Number of voxels	Brain regions included in cluster	Side	Coordinates (x, y, z)	Peak Z-value	P value (corrected)
4	Inferior parietal lobe	Right	50, –40, 44	5.00	< 0.05
4	Putamen	Right	22, 2, 0	5.23	< 0.05

metry in the planum temporale (Jernigan et al. 1991; Plante et al. 1991), and smaller pars triangularis with a reversed asymmetry (Gauger et al. 1997) have been reported. In addition, children with DLD had cytoarchitectural abnormalities (Galaburda et al. 1979, 1985; Cohen et al. 1989) and loss of leftward asymmetry in various areas (Herbert et al. 2005), which were closely similar to those in children with autistic disorder.

Functional imaging studies have been rarely attempted in children with DLD. Using Xenon-133 SPECT, Lou et al. (1984) reported symmetrical hypoperfusion in the perisylvian regions in 4 boys with phonologic-syntactic dysphasia (3 boys had comorbid attention deficit disorder) during the resting state (Lou et al. 1984). In their subsequent SPECT study with Xenon-133, 7 children with dysphasia, but without hyperactive behavior, had hypoperfusion in the left temporofrontal regions compared to control subjects (Lou et al. 1990). Among them, 4 children with decoding or lexical-semantic deficit showed hypoperfusion in the left central perisylvian region. In addition, 3 children with a phonologic-syntactic deficit showed hypoperfusion in the left prefrontal region. Using technetium-99m-HMPAO SPECT, Denays et al. (1989) found hypoperfusion in the left temporoparietal region and the upper and middle areas of the right frontal lobe during the resting state in 12 children with deficits in both comprehension and expression of language (Denays et al. 1989). In a recent Tc-99m HMPAO study, Ors et al. found that 19 children with DLD had significant hypoperfusion in the right parietal region and in the subcortical region including the thalamus and the basal ganglia during the resting state compared with 12 children with ADHD using a ROI analysis (Ors et al. 2005).

The differences in patterns of activation during a language task have also been reported in children with DLD (Tzourio et al. 1994; Bernal and Altman 2003; Liegeois et al. 2003). Using Xenon-133 SPECT, Tzourio et al. (1994) found that children with expressive-receptive deficits had an absence of left hemisphere activation during the phonemic discrimination tasks compared to both children with expressive deficits only and children with ADHD. They also observed an absence of activation in the left inferior parietal region in both children with expressive-receptive deficits and children with expressive deficits only. In fMRI study with a passive listening task, while children with normal speech had lateralized activation signal in the left hemisphere, children older than 3 years of age with DLD had activation in the right hemisphere (Bernal and Altman 2003). In a fMRI study of members in the KE family, 5 affected members had overactivation in the upper left and right postcentral gyrus and the left and right precentral gyrus during the task of covert generation of verbs in response to hearing nouns compared to 5 nonaffected members. They also had underactivation in the left and right inferior frontal gyrus, the upper part of left postcentral gyrus, and the right basal ganglia including the putamen and the globus pallidus during task of covert generation of verbs. In addition, affected members showed overactivation in the left anterior insular and underactivation in the left and right putamen during the task of overt generation and repetition of verbs (Liegeois et al. 2003).

Locations of the reported abnormal perfusion in children with DLD do not coincide from one study to another. The inconsistence may be partly explained by differences in age range and characteristics of the study population. Most subjects of previous studies were school-aged children, which makes it difficult to identify genuine functional deficits in children with DLD during earlier stages of language development. In previous studies, ADHD was often not considered as comorbidities or were even regarded as the control condition. However, ADHD frequently co-occur with language impairment (Beitchman et al. 1996) and might be contribute to mixed results in previous studies.

Our findings of hypoperfusion in the right putamen and the left globus pallidus are consistent with results of recent functional neuroimaging studies of DLD (Liegeois et al. 2003; Ors et al. 2005). The results of the current study may provide additional evidence for a suggested role of the basal ganglia in human language development (Lieberman 2002; Ulman and Pierpont 2005). Damage in the basal ganglia cause language abnormalities and diverse behavioral symptoms (Lieberman 2000; York et al. 2003). Moreover, abnormal development of the basal ganglia is involved in deficits that influence language production and syntax (Vargha-Khadem et al. 1998; Lal et al. 2001; Watkins et al. 2002). The putamen receives sensory inputs from most parts of the brain, and sends them to various brain areas including the globus pallidus. The putamen is comprised in the systems that sequence the submovements that together constitute overt movements in the brain. Moreover, the putamen has a projection to different parts of the brain, forming a number of circuits that regulate higher cognition, attention, reward-based learning, and language (Aldridge et al. 1993; Cunnington et al. 1995; Lieberman 2000; Marsden and Obeso 1994). The globus pallidus has been reported to have a role in the control of lexical-semantic operations and phonemic fluency (Nelson and McEvoy 1979; York et al. 2003). It has been proposed that idiosyncratic mappings are stored in a memorized "mental lexicon" that depends on declarative memory, whereas the learning and use of rule-governed computation involves a "mental grammar" that depends on procedural memory in which basal ganglia may play an important role (Ullman 2004; Ulman and Pierpoint 2005).

Smaller volume and hypoperfusion in the right inferior parietal cortex has been reported in previous studies (Jernigan et al. 1991; Ors et al. 2005), which were accord with the results of our study. Although functional role has not been reported in the right inferior parietal cortex during language processing, our current results may reflect either nonlingual deficits or a possible functional deficits during the resting state in children with DLD.

The limitations of our study are as follows. The first originates from the status of patients during the imaging process. The findings of this study are based on the resting state, but individual emotional and behavioral reactions to the imaging process could have affected our findings. We made an effort to control for patient status by creating a calm environment and by having mothers be with the child during the imaging acquisition process. However, a functional study using active cognitive tasks would be needed to overcome this limitation. The second limitation of our study was the selection of the control group. For ethical reasons, control subjects were selected retrospectively among children who had previously received SPECT. In addition, their age and gender could not be matched, which could confound our findings. Although even an adult control group has been used in previous pediatric SPM analysis (Chugani et al. 2001; Lee et al. 2005), control subjects in the current study were not optimal. We used the ANCOVA module in SPM in order to minimize age effects, but the specific effects of ANCOVA on imaging data analyses have not been discussed in previous studies. However, according to the results of PET studies in which the CMRGlc (regional cerebral metabolic rates for glucose) was estimated from the neonatal period to adolescence, brain metabolism might undergo 3 phasic patterns. From the neonatal period, brain metabolism increases rapidly, reaches a high plateau level from 4 to 12 years old, and then decreases from adolescence to adulthood (Bentourkia et al. 1998; Chugani 1998), which suggests that the SPECT data of our control subjects can be used in the current study. Moreover, we used a relatively stringent threshold (uncorrected p value < 0.001) and conducted additional analysis at the more conservative level of the threshold (corrected p value < 0.05).

Although the findings of our study should be interpreted with caution, they suggest that the basal ganglia and the inferior parietal lobe may be involved in the functional deficits of children with DLD during the resting state.

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