RESEARCH ARTICLE

Objective PET study of glucose metabolism asymmetries in children with epilepsy: Implications for normal brain development

Vinod K. Pilli^{1,3} | Jeong-Won Jeong^{1,2,3} | Praneetha Konka^{1,3} | Ajay Kumar^{1,2,3} | Harry T. Chugani^{1,2,3} | Csaba Juhász^{1,2,3}

¹The Carman and Ann Adams Department of Pediatrics, Wayne State University, Detroit, Michigan

²Department of Neurology, Wayne State University, Detroit, Michigan

³PET Center and Translational Imaging Laboratory, Children's Hospital of Michigan, Detroit, Michigan

Correspondence

Csaba Juhász, MD, PhD, Professor of Pediatrics and Neurology, Wayne State University School of Medicine, PET Center and Translational Imaging Laboratory, Children's Hospital of Michigan, 3901 Beaubien St., Detroit, MI 48201, USA.
Email: csaba.juhasz@wayne.edu

Present address

Harry T. Chugani, Division of Neurology, Nemours/Alfred I. DuPont Hospital for Children, Wilmington, DE, USA, and Department of Neurology, Thomas Jefferson University School of Medicine, Philadelphia, PA, USA

Funding information

National Institute of Neurological Disorders and Stroke, Grant/Award Numbers: NS041922, NS089659

Abstract

Clinical interpretation of cerebral positron emission tomography with 2-deoxy-2[F-18]fluoro-D-glucose (FDG-PET) images often relies on evaluation of regional asymmetries. This study was designed to establish age-related variations in regional cortical glucose metabolism asymmetries in the developing human brain. FDG-PET scans of 58 children (age: 1–18 years) were selected from a large single-center pediatric PET database. All children had a history of epilepsy, normal MRI, and normal pattern of glucose metabolism on visual evaluation. PET images were analyzed objectively by statistical parametric mapping with the use of age-specific FDG-PET templates. Regional FDG uptake was measured in 35 cortical regions in both hemispheres using an automated anatomical labeling atlas, and left/right ratios were correlated with age, gender, and epilepsy variables. Cortical glucose metabolism was mostly symmetric in young children and became increasingly asymmetric in older subjects. Specifically, several frontal cortical regions showed an age-related increase of left > right asymmetries (mean: up to 10%), while right > left asymmetries emerged in posterior cortex (including portions of the occipital, parietal, and temporal lobe) in older children (up to 9%). Similar trends were seen in a subgroup of 39 children with known right-handedness. Age-related correlations of regional metabolic asymmetries showed no robust gender differences and were not affected by epilepsy variables. These data demonstrate a region-specific emergence of cortical metabolic asymmetries between age 1–18 years, with left > right asymmetry in frontal and right > left asymmetry in posterior regions. The findings can facilitate correct interpretation of cortical regional asymmetries on pediatric FDG-PET images across a wide age range.

KEYWORDS

asymmetry, brain development, children, cortex, glucose metabolism, positron emission tomography

1 | INTRODUCTION

Positron emission tomography (PET) imaging with 2-deoxy-2[F-18]fluoro-D-glucose (FDG) has been used to study cerebral glucose metabolism for over 30 years. Detection of cortical glucose metabolic abnormalities can help in the management of a variety of neurological disorders, including pediatric epilepsy, where it can facilitate delineation of epileptic foci for resective surgery (Gaillard et al., 1995; Sood &

Chugani, 2006). Clinical evaluation of PET images largely relies on visual assessment of focal, regional, and hemispheric cortical asymmetries of FDG uptake. Differentiation of physiologic versus pathologic asymmetries in patients requires comparison to images from age-matched healthy controls. While such control data can be obtained in healthy adults, PET imaging in completely healthy children is difficult due to concerns of the effects of ionizing radiation (albeit a small dose) on the developing brain.

Due to the lack of true healthy pediatric control data, FDG-PET studies assessing maturation of cerebral glucose metabolism utilized "pseudo-control" groups, such as children with epilepsy (Chugani & Phelps, 1986; Chugani, Phelps, & Mazziotta, 1987; Muzik et al., 1998; Muzik et al., 1999; Van Bogaert, Wikler, Damhaut, Szliwowski, & Goldman, 1998), deaf children (Kang et al., 2004), children with suspected hypoxic-ischemic brain injury (Kinnala et al., 1996), and children with extracranial malignancy without brain involvement, where brain scans were acquired as a part of a whole-body PET/CT scan (Hua, Merchant, Li, Li, & Shulkin, 2015; London & Howman-Giles, 2015; Shan et al., 2014). Some of these studies utilized objective voxel-based analyses with statistical parametric mapping (SPM) that allowed the automated quantitative analysis of glucose uptake in different brain regions (London & Howman-Giles, 2015; Van Bogaert et al., 1998). SPM has also been used for detecting hypo- and hyper-metabolic clusters in children with medically refractory epilepsy undergoing presurgical evaluation of FDG-PET with the use of adult healthy or pseudo-normal pediatric control PET data (Archambaud et al., 2013; Jeong et al., 2017; Kumar et al., 2010).

While the maturational changes of absolute and relative regional glucose metabolism in the developing human brain has been described extensively (Chugani et al., 1987; Chugani & Phelps, 1986; London & Howman-Giles, 2015; Van Bogaert et al., 1998), the effect of age on regional glucose metabolic asymmetries has not been evaluated in children. To fill this gap, in this study, we analyzed cerebral regional glucose metabolic asymmetries and their variations with chronological age from brain FDG-PET scans of children, age 1–18 years, with non-lesional epilepsy and normal brain glucose metabolic pattern on visual evaluation, using images selected from a large single-center pediatric PET database. We also evaluated if the observed variations of regional metabolic asymmetries are affected by gender or epilepsy variables. The obtained data could be useful to assist a refined assessment of pediatric cerebral FDG-PET images and facilitate correct clinical interpretation of mild regional asymmetries of FDG uptake, for example, during presurgical evaluation of epilepsy. The data could also provide an insight in metabolic correlates of maturation of lateralized brain functions during human brain development.

2 | MATERIALS AND METHODS

2.1 | Subjects

From our pediatric database of ~1,500 PET scans, performed at the PET Center, Children's Hospital of Michigan, we first identified 185 images reported to have a normal glucose metabolic pattern on the original clinical PET report generated by a single investigator (HTC). After reviewing electro-clinical data, MRI, and PET images of these patients, we identified a total of 58 children (age: 1–18 years [mean: 9.3 ± 5.3 years], Table 1) who fulfilled the following inclusion criteria: (1) normal glucose metabolic pattern on visual PET assessment based on re-review of all of the 185 PET images by two of the authors (AK and CJ); only images confirmed to be normal by both investigators were included, (2) normal clinical MRI, (3) absence of seizures, frequent epileptiform activity, or severe slowing of background

activity on scalp EEG recorded during the FDG uptake period. Exclusion criteria were as follows: (1) severe comorbidity such as history of clinically significant cognitive/developmental delay, autism, depression, cerebral palsy, or known genetic disorders including mitochondrial disorders, (2) high seizure frequency (daily or more frequent seizures) or known clinical seizures within 24 hr before the PET scan. All selected patients had a history of epilepsy and were on antiepileptic medication in mono- or polytherapy (Table 1). None of the children underwent epilepsy surgery before or after the PET scan. Retrospective review of clinical data and analysis of clinically acquired, deidentified images for these studies were performed based on a protocol approved by the Wayne State University Institutional Review Board.

2.2 | PET image acquisition

All PET studies were performed with clinical indication using a GE Discovery STE PET/CT, located at the PET Center, Children's Hospital of Michigan, Detroit, MI. The scanner combines a Light-Speed 16-slice CT with an advanced BGO PET system yielding 47 image planes with a 16 cm axial field-of-view (FOV). The reconstructed image in-plane resolution is 5.5 ± 0.35 mm at full-width-at-half-maximum (FWHM) and 6.0 ± 0.49 mm in the axial direction (reconstruction parameters: Shepp-Logan filter with 0.3 cycles/pixel cutoff frequency). All subjects fasted for at least 6 hr prior to the PET procedure. EEG was monitored using surface electrodes during the entire FDG uptake period to ensure interictal scans. A venous line was established for tracer injection (0.141 mCi/kg FDG). During the FDG uptake period external stimuli were minimized by dimming the lights and discouraging interaction, so that studies reflected the resting awake state. Forty minutes after FDG injection, a static 20-min emission scan of the brain was acquired in 3D mode.

For the PET scanning period (but not during FDG uptake), most children below 12 years of age were sedated with pentobarbital (1.5 – 3 mcg/kg) and midazolam (0.1 – 0.2 mcg/kg); or by midazolam (0.1 – 0.2 mcg/kg) followed by dexmedetomidine (1 – 2 mcg/kg), titrated slowly to achieve mild to moderate sedation. All subjects were continuously monitored by a pediatric nurse, and physiological parameters (heart rate, pulse oximetry) were measured throughout the study.

2.3 | PET image analysis

SPM Diffeomorphic Anatomical Registration Through Exponential Lie Algebra (DARTEL, www.fil.ion.ucl.ac.uk) procedure (Ashburner, 2007) was applied to create five age-specific FDG PET templates from the 58 FDG PET images for children 1–3, 3–6, 6–10, 10–14, and 14–18 years of age. Using the DARTEL deformation toolbox, the deformation field was applied to the adult AAL template, where the deformation field was obtained between our pediatric PET template and SPM adult PET template. By adjusting both the inner iteration number and regularization parameter, we could obtain an accurate deformation field between the adult PET template and our own PET template, including the youngest age group (1–3 years). These two parameters were optimized using an in-house MATLAB script in the framework of a generalized pattern search algorithm to minimize least mean square error between the deformed adult PET template and our

TABLE 1 Demographic and clinical data of 58 children with epilepsy and normal FDG-PET

Pt	Sex	Age at scan (months)	Age at onset (months)	Duration of epilepsy (months)	Seizure type	Handedness	PET-EEG	Routine EEG/VMR	No. of AEDs	Post-PET follow-up (years)	Epilepsy course
1	F	12	8	4	GTCS	4	Normal	Normal	2	3.6	Stable
2	M	14	4	10	CPS	1	Normal	Normal	2	9.4	Stable
3	F	19	12	7	CPS	4	Normal	Normal	2	4.5	Improved
4	M	22	6	16	CPS	1	Normal	Normal	2	5.7	Improved
5	F	24	12	12	CPS	4	Normal	Normal	1	5.0	Improved
6	M	31	19	12	CPS	4	Normal	Normal	2	4.3	Resolved
7	F	33	10	23	IS	3	Normal	Normal	1	0.5	Improved
8	M	33	19	14	GTCS	3	Normal	Normal	2	0.9	Improved
9	M	36	24	12	CPS	3	Normal	Normal	2	0.7	Stable
10	M	38	28	10	CPS	1	Normal	Normal	2	10	Resolved
11	M	41	17	24	GTCS	1	3 Hz gen. s/w	3 Hz gen. s/w	1	1.9	Resolved
12	M	42	18	24	CPS	1	Normal	Gen. s/w	2	4.8	Resolved
13	F	42	16	26	CPS	1	Normal	Normal	2	4.5	Resolved
14	F	50	14	36	AS	1	3 Hz gen. s/w	3 Hz gen. s/w	1	5.3	Stable
15	M	54	42	12	MS	2	Normal	Normal	1	5.0	Resolved
16	F	56	8	48	GTCS	1	Normal	Gen. s/w	2	8.4	Stable
17	F	60	14	46	CPS	1	Normal	Normal	1	4.6	Resolved
18	M	63	39	24	GTCS	1	Normal	Normal	1	4.0	Improved
19	M	73	49	24	GTCS	3	Gen. s/w	Gen. s/w	3	4.2	Improved
20	M	78	75	3	NA	1	Normal	Lt P	1	0.3	Stable
21	F	80	0	80	GTCS	1	Normal	Normal	1	0.4	Stable
22	F	83	3	80	GTCS	1	Normal	Normal	1	10	Stable
23	F	87	27	60	GTCS	1	3 Hz gen. s/w	3 Hz gen. s/w	2	n/a	n/a
24	F	88	6	82	GTCS	1	Gen. s/w	Gen. s/w	1	9.3	Improved
25	F	89	77	12	CPS	1	Normal	Normal	2	9.5	Improved
26	F	89	53	36	CPS	1	Rt T	Gen. s/w	2	9.0	Improved
27	F	92	20	72	CPS	4	Normal	Normal	1	10	Resolved
28	M	95	41	54	GTCS	1	Rt T	Normal	3	7.5	Resolved
29	F	98	65	33	AS	1	3 Hz gen. s/w	n/a	3	4.9	Improved
30	M	100	90	10	CPS	4	Normal	Lt TP	3	7.5	Stable
31	M	102	66	36	CPS	1	Normal	Normal	1	5.0	Stable
32	M	111	6	105	CPS	1	Normal	Rt T	1	5.2	Stable
33	M	114	104	10	GTCS	4	Normal	Normal	2	0.3	Nonepi
34	F	124	17	107	CPS	1	Normal	Normal	4	n/a	n/a
35	M	129	81	48	CPS	1	Normal	Normal	2	0.8	Improved
36	F	135	83	52	AS	2	Normal	Lt T	2	5.5	Resolved
37	M	144	NA	NA	NA	1	Normal	Lt TP	2	6.4	Resolved
38	M	147	75	72	CPS	2	Normal	Lt + rt TP	1	5.7	Stable
39	F	151	NA	NA	NA	4	Normal	n/a	0	n/a	n/a
40	F	156	108	48	GTCS	1	Gen. s/w	Gen. s/w	1	n/a	n/a
41	F	162	150	12	CPS	1	Normal	Normal	1	7.0	Resolved
42	M	162	102	60	CPS	1	Normal	Lt T	1	6.0	Resolved
43	F	164	140	24	CPS	1	Normal	Normal	1	3.2	Resolved
44	F	175	157	18	CPS	4	Normal	Gen. s/w	2	n/a	n/a
45	F	176	104	72	GTCS	4	Normal	Normal	1	2.3	Stable
46	M	180	2	178	CPS	4	Normal	n/a	1	0.3	Stable
47	F	180	140	40	CPS	1	Gen. s/w	Gen. s/w	2	2.1	Stable
48	M	183	111	72	CPS	1	Normal	Lt TP	2	3.7	Resolved
49	M	188	8	180	CPS	1	Normal	Bi FP	2	6.7	Stable
50	M	193	188	5	NA	1	Normal	Normal	1	n/a	n/a

(Continues)

TABLE 1 (Continued)

Pt	Sex	Age at scan (months)	Age at onset (months)	Duration of epilepsy (months)	Seizure type	Handedness	PET-EEG	Routine EEG/VMR	No. of AEDs	Post-PET follow-up (years)	Epilepsy course
51	M	196	NA	NA	NA	4	Bi F	Bi F	3	n/a	n/a
52	F	197	161	36	GTCS	1	Normal	Normal	3	2.5	Improved
53	F	200	188	12	CPS	1	Normal	Normal	3	0.5	Improved
54	M	204	NA	NA	CPS	1	Normal	Normal	1	1.7	Improved
55	F	210	162	48	GTCS	1	Normal	Normal	2	4.7	Resolved
56	M	212	140	72	CPS	1	Normal	Na	2	0.3	Stable
57	M	213	138	75	CPS	1	Normal	Rt F + Lt T	2	1.2	Stable
58	F	216	156	60	GTCS	1	Gen. s/w	Normal	1	1.5	Stable

Note. Abbreviations: AED = anti epileptic drugs; AS = absence seizures; Bi = bilateral; CPS = complex partial seizures; F = female; F = frontal; gen. = generalized; GTCS = generalized tonic-clonic seizures; IS = infantile spasms; Lt = left; M = male; MS = myoclonic seizures; n/a = not available; P = parietal; PET-EEG = EEG during PET scan; Pt = patient; rt = right; s/w = spike and wave; T = temporal; VMR = video EEG monitor recording. The subjects are listed from the youngest to the oldest. Handedness: 1, right; 2, left; 3, ambidextrous; 4, unknown. Epilepsy course refers to the period of post-PET follow-up (where available). Epilepsy was considered to be improved, if the seizure frequency decreased by at least 50%; and resolved if the child was seizure-free for at least 2 years at the last follow-up.

pediatric template. The reliability of such age-specific pediatric PET templates has been demonstrated by our group to detect hypo- and hypermetabolic cortical regions in children with epilepsy undergoing epilepsy surgery, including those below 4 years of age (Jeong et al., 2017). The resulting age-specific templates were then used as standard brain space to spatially normalize PET images of individual pseudo-normal controls using SPM 8 DARTEL deformation toolbox.

To parcellate regions of interest (ROIs) in each age-specific FDG-PET template, we utilized an automated anatomical labeling atlas (AAL, <http://www.gin.cnrs.fr/en/tools/aal-aal2/>) consisting of 90 cerebral parcellations in standard template space in whole cerebral cortex and deep nuclei (45 in each hemisphere). The ROIs of this AAL template were spatially transferred to each of the age-specific FDG-PET templates using the SPM 8 DARTEL deformation toolbox. Deep nuclei were not included in the analysis. In addition, cortical AAL regions with small volumes and/or small diameter, located deeply and close to the midline, were also excluded from the analysis to minimize partial volume effects and the uncertainty of accurate asymmetry assessments. The remaining 35 age-specific cortical AAL ROI pairs were applied to the spatially normalized FDG-PET images of individual patients to obtain mean voxel intensity values for each individual ROI, calculated after proportional normalization to whole brain activity. Finally, regional left/right ratios from homotopic corresponding regions were calculated to characterize asymmetries.

2.4 | Statistical analysis

First, mean left/right glucose uptake ratios in all 35 brain regions were calculated in three broad age groups: (1) 1–6 years, (2) 6–12 years, and (3) 12–18 years, with 18–21 subjects in each group. Subsequently, the left/right regional FDG uptake ratios were correlated with age at scan, duration of epilepsy, and age at onset of epilepsy, using Pearson's correlations. Multivariate regression analysis was also performed to assess the effect of age versus these epilepsy variables. These tests were performed both in the whole group, in male and female subgroups ($n = 29$ each), as well as in a subgroup of children where right handedness could be confirmed based on parent interviews and neurological examination ($n = 39$). p values were corrected

for multiple comparisons using false discovery rate (FDR) correction (Benjamini & Hochberg, 1995). Statistical analysis was carried out using SPSS 24.0 (IBM Corp., Armonk, NY). The differences between corresponding correlation coefficients calculated in males versus females were compared as described by Cohen, Cohen, West, and Aiken (2003). p values $< .05$ were considered significant.

3 | RESULTS

3.1 | Clinical and EEG data

Epilepsy variables and EEG data are summarized in Table 1. Common seizure types included focal ($N = 31$) or generalized tonic-clonic seizures ($N = 17$), while a few patients had a history of absence seizures, myoclonic seizures or infantile spasms; five patients had unknown seizure semiology. Most patients had multiple EEGs available and showed no epileptiform activity on any of those in the majority of the patients (32/58, 55%), while EEGs recorded during the FDG uptake period were completely normal in 46 cases (79%), and showed focal lateralized epileptiform activity in only 2 cases (Table 1).

3.2 | Regional left/right asymmetries in three age groups

Mean left/right asymmetries in all 35 AAL regions in the three age groups are shown in Table 2. In general, left > right asymmetries were most commonly present in frontal regions; mean left/right ratio reached or exceeded 1.05 (i.e., 5% asymmetry) in none of the regions in children below 6 years of age, in 3 frontal regions in those 6–12 years of age, and in 4 frontal regions in those above age 12 years. In contrast, right > left FDG uptake ratios were most common in posterior (parieto-occipital) regions, with mean left/right ratios reaching 0.95 or below in 2 regions in the youngest subgroup (age below 6 years), in 4 regions in those age 6–12 years, and in 7 regions in those above 12 years of age. Altogether, in children above 12 years of age, 11/35 regions showed a mean asymmetry of 5% or above. Two regions (middle frontal and superior medial frontal) showed the

TABLE 2 Mean and standard deviation (SD) of left/right asymmetries of regional FDG uptake in three age groups

Cortical region	Age 1–6 (N = 18) Mean	SD	Age 6–12 (N = 19) Mean	SD	Age 12–18 (N = 21) Mean	SD
Precentral gyrus	0.98	0.02	1.01	0.02	0.97	0.03
Superior frontal gyrus, dorsolateral	1.00	0.02	1.02	0.02	1.00	0.02
Superior frontal gyrus, orbital part	0.99	0.02	1.02	0.03	1.05	0.03
Middle frontal gyrus	1.01	0.02	1.09	0.03	1.10	0.02
Inferior frontal gyrus, opercular part	0.96	0.03	0.97	0.03	0.98	0.04
Inferior frontal gyrus, triangular part	1.01	0.03	1.06	0.03	1.08	0.03
Inferior frontal gyrus, orbital part	0.99	0.03	0.98	0.04	1.03	0.04
Rolandic operculum	0.99	0.03	1.01	0.02	0.99	0.03
Supplementary motor area	1.00	0.02	1.00	0.02	1.00	0.03
Superior frontal gyrus, medial	1.02	0.03	1.08	0.02	1.10	0.03
Frontal medial orbital gyrus	0.99	0.03	0.95	0.03	0.95	0.03
Gyrus rectus	0.96	0.03	0.95	0.03	0.97	0.02
Insula	1.02	0.03	1.03	0.02	1.01	0.03
Anterior cingulate and paracingulate gyri	0.98	0.03	1.02	0.02	1.01	0.02
Hippocampus	1.01	0.02	1.03	0.02	1.02	0.03
Parahippocampal gyrus	1.00	0.03	0.98	0.03	0.99	0.03
Calcarine	0.99	0.02	0.97	0.02	0.95	0.03
Cuneus cortex	0.99	0.03	1.01	0.04	1.00	0.04
Lingual gyrus	0.99	0.02	1.00	0.02	0.98	0.02
Superior occipital gyrus	0.92	0.03	0.93	0.02	0.94	0.03
Middle occipital gyrus	0.98	0.03	0.95	0.02	0.95	0.02
Inferior occipital gyrus	0.99	0.03	1.04	0.05	0.99	0.04
Fusiform gyrus	1.00	0.03	1.00	0.03	1.00	0.03
Postcentral gyrus	0.97	0.02	0.97	0.02	0.98	0.03
Superior parietal gyrus	0.99	0.03	1.01	0.04	1.04	0.06
Inferior parietal, excluding supramarginal, and angular	0.95	0.03	0.97	0.03	0.95	0.03
Supramarginal gyrus	0.98	0.03	0.99	0.03	1.00	0.04
Angular gyrus	0.99	0.03	0.95	0.03	0.91	0.04
Precuneus	0.99	0.02	0.96	0.02	0.95	0.03
Paracentral lobule	0.99	0.04	0.98	0.05	1.04	0.07
Superior temporal gyrus	0.99	0.02	1.02	0.02	1.01	0.02
Temporal pole, superior temporal gyrus	0.99	0.05	1.02	0.05	1.04	0.06
Middle temporal gyrus	0.99	0.02	0.98	0.03	0.96	0.03
Temporal pole, middle temporal gyrus	1.00	0.06	1.00	0.07	0.99	0.06
Inferior temporal gyrus	1.01	0.05	0.98	0.04	0.99	0.03

highest mean left/right ratio (1.10 in both) in the whole group (-Table 2). The single highest individual left/right asymmetry value in both regions was 1.15.

3.3 | Correlation of regional cortical glucose uptake asymmetries with age in the whole group

Out of the 35 individual regional asymmetries, 15 showed a significant correlation with age after FDR-correction: 9 of these correlations were positive and 6 regions showed an inverse correlation with age (Table 3). The most robust age-related positive correlations were found in several regions of the frontal lobe, due to largely symmetric glucose uptake in the youngest subjects and a gradual emergence of a left > right asymmetry by 18 years of age (Figures 1 and 2).

Additional, although weaker, positive correlations were found in the superior parietal cortex, temporal pole (superior portion), and paracentral lobule (Table 3).

An opposite, *inverse correlation* between age and FDG uptake asymmetries was detected mostly in posterior regions (Table 3), including middle occipital and calcarine cortex, angular gyrus, precuneus, and middle temporal gyrus, indicating an age-related emergence of right > left asymmetry in these regions (Figure 3). The only anterior region that showed a moderate inverse correlation with age ($r = -.38$) was the frontal medial orbital cortex in the whole group, although this region showed no significant age-related variation in the right-handed subgroup (see details below).

TABLE 3 Age-related correlations in regional left/right asymmetries in the whole group ($N = 58$)

Whole group ($N = 58$)			
Cortical region	r value	p value	Slope
Superior frontal, orbital part	0.66	<.001	0.0049
Middle frontal	0.75	<.001	0.0064
Inferior frontal, triangular part	0.64	<.001	0.0046
Inferior frontal, orbital part	0.44	.001	0.0037
Superior frontal, medial	0.8	<.001	0.0062
Frontal, medial orbital	−0.38	.008	−0.0025
Anterior cingulate/paracingulate	0.45	.001	0.0024
Calcarine	−0.56	<.001	−0.0029
Middle occipital	−0.54	<.001	−0.0026
Superior parietal	0.46	.001	0.0041
Angular	−0.69	<.001	−0.0059
Precuneus	−0.62	<.001	−0.0030
Paracentral lobule	0.41	.004	0.0046
Temporal pole, superior	0.37	.01	0.0038
Middle temporal	−0.57	<.001	−0.0033

Note. Only regions with significant correlations (after false discovery rate correction) are shown. The slopes of the linear regression lines were calculated from with age entered in years.

Some regional asymmetries also showed a correlation with duration of epilepsy and/or age at seizure onset. However, in the multivariate regression analysis, only age at the time of the PET scan remained significantly associated with asymmetries (in the same regions as above).

3.4 | Gender comparisons

Regions showing age-related significant correlations in males and females are listed in Table 4. In most of these regions (including several frontal areas and the superior parietal cortex), the correlation coefficients were higher in males than females. However, the differences were not statistically significant, although four regions showed a statistical trend ($p < .1$; Table 4).

3.5 | Subgroup analysis in right-handed children

Of the 58 children, 39 (67%) were confirmed right-handed, 3 children (5.2%) were left-handed, and 4 children were ambidextrous, while handedness was unknown in the remaining 12 subjects. In the right-handed subgroup, 15 out of 35 individual regional left/right metabolic asymmetries showed a significant correlation with age at scan (Table 5). Overall, these correlations were similar to those found in the whole group; however, while negative correlations were confined to posterior regions only (not including any frontal region), positive correlations also included the rectal gyrus. Again, the age-related correlations remained significant when epilepsy variables were entered in a multivariate regression. There were no significant gender differences when correlation coefficients were compared between right-handed males and females (Table 6).

4 | DISCUSSION

Our findings demonstrate a developmental trajectory of metabolic asymmetries, with an overall increase in regional asymmetries as the brain matures: in the frontal cortex, a leftward metabolic asymmetry emerged, whereas in several posterior brain regions, particularly in the occipital cortex, an opposite, right > left asymmetry developed by adolescence. These age-related variations appeared to be similar in both genders, although somewhat stronger in males, especially in the frontal regions. Also, the age-related correlations were not affected by clinical epilepsy variables. Further, the majority of the patients had normal EEGs, and only three subjects had focal lateralized epileptiform abnormality on their PET-EEG. Thus, it is reasonable to assume that the observed age- and region-dependent metabolic asymmetries largely reflect physiologic developmental changes rather than epilepsy-related abnormalities. Age-related emergence of these asymmetries may reflect an increasing hemispheric functional specialization. Knowledge of these developmental metabolic asymmetries can improve the accuracy of clinical assessment of brain FDG PET images in pediatric neurological disorders.

FIGURE 1 FDG-PET images of four children (age range: 1.8–13.7 years) showing almost symmetric frontal cortical glucose uptake in the two younger subjects and asymmetric frontal cortical uptake (left > right) in the two older children. On SPM analysis, the middle frontal gyrus showed a left/right ratio of 0.98 in the two younger patients, 1.08 in the 7.3-year old, and 1.15 in the oldest child. The images are shown with an individualized, relative color scale, with red representing the highest (100%) and black the lowest values (0%) [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 2 Scatter plots showing age-related increases of left/right ratios of regional FDG uptake in two frontal lobe regions between age 1 and 18 years. The left panels show correlations in the whole group ($N = 58$) and the right panels include only right-handed children ($N = 39$) [Color figure can be viewed at wileyonlinelibrary.com]

4.1 | Cortical morphologic asymmetries during normal brain development and in the epileptic brain

MRI studies of cortical hemispheric structural asymmetries in the developing brain demonstrated increasing structural asymmetries as the child grows older, with continuing changes throughout adolescence extending into adulthood (Plessen, Hugdahl, Bansal, Hao, & Peterson, 2014; Shaw et al., 2009; Zhou, Lebel, Evans, & Beaulieu, 2013). However, there were discrepancies across studies involving various (although overlapping) age groups. For example, a study of young adults reported a significant leftward asymmetry in cortical thickness in precentral, middle frontal, anterior temporal, and superior parietal regions, and a rightward asymmetry in postero-inferior temporal and inferior frontal regions (Luders et al., 2006). A subsequent longitudinal MRI study reported a prominent interaction between age and cortical thickness asymmetry in 358 typically developing children (age: 3–22 years), where a right > left cortical thickness asymmetry developed in the inferior frontal gyrus and lateral orbitofrontal cortex, extending into the insula (Shaw et al., 2009); this coincided with the emergence of a left > right thickness asymmetry in posterior regions. A third study, involving 274 right-handed healthy participants (age 5–59 years) demonstrated limited cortical asymmetries before adolescence (right > left in the inferior frontal gyrus and medial occipital lobe), but more extensive side differences after adolescence into

adulthood, when more extensive frontal and parietal asymmetries emerged (Zhou et al., 2013).

To address the partial discrepancies among these previous studies, Plessen et al. (2014) assessed cortical asymmetries in 215 healthy children and adults, age 7–59 years. They found left > right asymmetry in cortical thickness throughout the entire lateral, dorsal, and medial surface of the frontal lobe, extending into primary sensory, superior parietal, and anterior superior temporal cortices. An opposite, right > left asymmetry was present in the posterior temporal, parietal, and occipital cortices, as well as in the entire inferior surface of the brain. In this latter study, there were also some gender effects, with the left > right asymmetries being more prominent in females, while the right > left asymmetries in the posterior brain regions being greater in males. The authors speculated that these gender differences may indicate the neuroanatomical correlates of the differences in cognitive abilities across genders, a female advantage on verbal tasks, and a male advantage on visuospatial tasks.

4.2 | Age-related changes of regional glucose metabolism in the present cohort

Regional cortical glucose metabolism can be affected by brain morphology including cortical volume and thickness. The age-related regional differences in glucose metabolic asymmetries, found in this

FIGURE 3 Scatter plots showing age-related decreases of left/right ratios of regional FDG uptake in the middle temporal and angular gyri between age 1 and 18 years. The left panels show correlations in the whole group ($N = 58$) and the right panels include only right-handed children ($N = 39$) [Color figure can be viewed at wileyonlinelibrary.com]

study, are partly consistent with the above MRI data, although several discrepancies can be observed. First, we detected the dominance of left > right glucose uptake in widespread frontal cortical regions, which increased with age and included regions involved in language function. This may represent an increasing functional asymmetry for expressive language as demonstrated by previous functional MRI and activation PET studies (Horwitz et al., 2003; Rutten, van Rijen, van Veelen, & Ramsey, 1999). The only exception was the medial orbital frontal cortex, a region that showed a moderate negative age-correlation in the whole group, although no significant age-correlation was present in right-handed children. In this latter subgroup, inverse age-related correlations, indicating a right > left emergence in older children, were confined to posterior brain regions such as parts of the occipital, temporal cortex, and angular gyrus (Table 5).

The partial overlap between structural and metabolic age-related asymmetries might be explained by several factors. First, the similarities may reflect the fact that thinner cortical regions may show lower metabolism on PET, partly because of partial volume effects. Age-related parallel changes in morphology and metabolism have been found in cognitively healthy adults by direct comparison of FDG-PET and MRI (Kakimoto et al., 2016). Also, variations in glucose metabolism corresponded well with volumetric changes in widespread cortical regions in patients with

amyotrophic lateral sclerosis and frontotemporal dementia, although additional metabolic abnormalities occurred in some regions with normal gray matter volume (Rajagopalan & Pioro, 2015).

In normal aging and neurological disorders associated with brain atrophy and marked cortical thinning, correction for partial volume effects can facilitate an accurate estimation of regional metabolic values (Kochunov et al., 2009; Park et al., 2006). While the patients included in this study had no visible brain atrophy, the epileptic brain can show subtle cortical changes in the form of cortical thinning. For example, in a study of children with new-onset epilepsy, a reduction of cortical thickness was reported in the bilateral frontal and right parietal cortex (Widjaja et al., 2012). Furthermore, in children with intractable frontal lobe epilepsy, bilateral cortical thinning was present in multilobar regions regardless of the actual side of the presumed epileptic focus (Widjaja, Mahmoodabadi, Snead, Almehdar, & Smith, 2011). Thus, it is possible that some of the cortical metabolic values have been affected by epilepsy-related cortical thinning in our cohort. Nevertheless, such changes likely would be mostly bilateral affecting asymmetry measures to a lesser degree. Future studies could compare such metabolic asymmetries to corresponding asymmetries and age-related changes in cortical morphology measured from the same subject to further refine the interpretation of our findings.

TABLE 4 Age-related correlations in regional left/right asymmetries in male versus female subjects

Cortical region	Males (N = 29)		Females (N = 29)		Difference between Corr. coefficients (p value)
	r value	p value	r value	p value	
Superior frontal, orbital part	0.77	<.001	0.57	.028	.17
Middle frontal	0.81	<.001	0.55	.028	.06
Inferior frontal, triangular part	0.79	<.001	0.51	.028	.05
Inferior frontal, orbital part	0.57	.012	0.44	.060	.51
Superior frontal, medial	0.74	<.001	0.73	<.001	.93
Frontal, medial orbital	−0.45	.045	0.03	.895	.06
Gyrus rectus	0.46	.043	0.45	.051	.97
Anterior cingulate/paracingulate	0.59	.011	0.17	.49	.07
Calcarine	−0.65	.004	−0.48	.036	.37
Middle occipital	−0.47	.042	−0.42	.073	.82
Inferior occipital	−0.21	.382	−0.51	.028	.21
Superior parietal	0.57	.013	0.34	.15	.29
Angular	−0.75	<.001	−0.56	.028	.21
Paracentral lobule	0.34	.142	0.53	.028	.40
Precuneus	−0.58	.012	−0.45	.051	.52
Temporal pole, superior temporal	0.52	.025	0.44	.057	.72
Middle temporal	−0.49	.033	−0.66	.007	.35

Note. Only regions with significant correlations (after false discovery rate correction) in at least one of the genders are listed. Gender differences between correlation coefficients did not reach significance in any of the regions.

4.3 | Potential clinical significance of the findings

An obvious practical implication of our findings is an improved assessment of cortical metabolic asymmetries on pediatric FDG-PET scans, for example, during presurgical evaluation. Many of these patients have no obvious lesions on MRI, and interpretation of mild/moderate cortical metabolic asymmetries on PET is a common clinical challenge. Previous PET studies in pediatric epilepsy typically used asymmetries of 10%–15% as a cutoff threshold to detect regional metabolic abnormalities in the presumed epileptic hemisphere (da Silva, Chugani, Muzik, & Chugani, 1997; Gaillard et al., 2002; Gaillard et al., 2007). Our data suggest that such asymmetry thresholds are generally appropriate in older children, especially for left > right asymmetries in the frontal cortex, superior parietal region, and temporal pole; and for right > left asymmetries in the middle occipito-temporal area, angular gyrus, and precuneus. On the other hand, even relatively minor (<10%) asymmetries may be considered as abnormal in some other regions, especially in young children.

We found no robust gender differences in the observed age-related variations of glucose metabolic asymmetries, although some statistical trends were observed in a few regions in the frontal lobe and with stronger age-related correlations in the male subgroup. This suggests that interpretation of asymmetries on FDG-PET should be less affected by gender.

4.4 | Study limitations

Our study has several limitations. First, the subjects of this study were epileptic children, where cortical asymmetries may be affected by epileptic foci. Although this effect could not be completely excluded, we believe that the observed age-related asymmetries were not driven by epileptic regions. This is supported by the fact that none of the PET

asymmetries correlated with clinical epilepsy variables in multivariate regressions. Furthermore, the majority of the children had normal EEGs, and only a fraction had focal, lateralized epileptiform EEG abnormalities. In particular, focal EEG abnormalities were not present in occipital regions and were extremely rare (1/58) in frontal cortex, which showed the greatest metabolic asymmetries. This makes it unlikely that focal epileptic abnormalities had a major effect on the observed robust age-related variations in regional FDG-PET asymmetries.

TABLE 5 Age-related correlations in regional left/right asymmetries in the right-handed subgroup (N = 39)

Right-handed subgroup (N = 39)		
Cortical region	r value	p value (FDR-corrected)
Superior frontal, orbital part	.68	<.001
Middle frontal	.69	<.001
Inferior frontal, triangular part	.63	<.001
Inferior frontal, orbital part	.50	.004
Superior frontal, medial	.73	<.001
Gyrus rectus	.46	.009
Anterior cingulate/paracingulate	.39	.030
Calcarine	−.57	.001
Middle occipital	−.45	.011
Superior parietal	.46	.009
Angular	−.68	<.001
Precuneus	−.50	.004
Paracentral lobule	.42	.018
Temporal pole, superior temporal	.47	.008
Middle temporal	−.56	.001

Note. Only regions with significant correlations (after false discovery rate [FDR] correction) are shown.

TABLE 6 Age-related correlations in regional left/right asymmetries in right-handed male versus female subjects

Cortical region	Males (N = 20)		Females (N = 19)		Difference between corr. coefficients (p value)
	r value	p value	r value	p value	
Superior frontal, orbital part	.77	<.001	.57	.02	.27
Middle frontal	.81	<.001	.55	.03	.13
Inferior frontal, triangular part	.79	<.001	.51	.04	.12
Inferior frontal, orbital part	.57	.015	.44	.06	.61
Superior frontal, medial	.74	<.001	.73	<.001	.94
Frontal, medial orbital	-.45	.04	.03	.9	.14
Gyrus rectus	.46	.04	.45	.05	.97
Anterior cingulate/paracingulate	.59	.015	.17	.49	.14
Calcarine	-.65	<.001	-.48	.04	.47
Middle occipital	-.47	.04	-.42	.07	.86
Inferior occipital	-.21	.38	-.51	.04	.31
Superior parietal	.57	.015	.34	.15	.41
Angular g	-.75	<.001	-.56	.02	.32
Precuneus	-.58	.015	-.45	.05	.62
Paracentral lobule	.34	.14	.53	.03	.51
Temporal pole, superior temporal	.52	.02	.44	.06	.78
Middle temporal	-.49	.03	-.66	<.001	.45

Note. Only regions with significant correlations (after false discovery rate correction) in at least one of the genders are listed. Gender differences between correlation coefficients did not reach significance in any of the regions.

Our study group included children as young as 1 year of age, whose overall brain volume is lower than the volume of older children. To address this issue, we utilized age-specific PET templates for SPM analyses. We have recently demonstrated the feasibility of this approach in analyzing PET scans of children with epilepsy above 1 year of age (Jeong et al., 2017). We used SPM automated anatomical labeling atlas consisting of cerebral parcellations including small regions in standard template space in whole cerebral cortex, an approach that was previously utilized in SPM analysis of PET scans of children with extracranial malignancies (London & Howman-Giles, 2015). We excluded the smallest regions (mostly deep, close to the midline) from the analysis where erroneous measures are most likely. In addition, our study relied on asymmetries of cerebral glucose metabolism. This approach helps diminish the potential confounding effects of variable medications that may affect cortical metabolism or thickness (Pardoe, Berg, & Jackson, 2013). Furthermore, handedness could not be established in a number of cases. This, however, is unlikely to have had a major effect on our results, considering that the main findings were similar both in the whole group and in the right-handed subgroup. The number of left-handed subjects was too low to allow a reliable separate analysis. The effect of handedness has not been addressed in previous, larger studies analyzing FDG uptake and asymmetries in healthy subjects, as these included only right-handed individuals or did not report on the handedness of the subjects (Wang, Volkow, Wolf, Brodie, & Hitzemann, 1994; Murphy et al., 1996; Ivancević et al., 2000; Kim, Kim, & Kim, 2009; London & Howman-Giles, 2015; Hua et al., 2015). Interestingly, in a recent large MRI study, assessing cortical brain asymmetries from 17,141 healthy subjects, the authors did not find significant associations with handedness (Kong et al., 2018). However, such large data sets are not available for FDG PET studies, and, therefore, it remains unknown if left-handedness would alter the observed age-related variations of metabolic asymmetries. Finally, our

study made inferences about longitudinal metabolic changes from a cross-sectional data set. However, acquisition of longitudinal FDG-PET data in a pediatric population is difficult due to ethical constraints of using PET in children outside the clinical setting.

4.5 | Conclusion

These findings demonstrate a robust, age-related, region-specific evolution of cortical glucose metabolic asymmetries in children between ages 1 and 18 years. Such age-specific metabolic asymmetry data may facilitate a more accurate clinical interpretation of pediatric brain FDG-PET images in children.

ACKNOWLEDGMENT

The study was partly funded by grants from National Institute of Neurological Disorders and Stroke (R01 NS089659 to J.J. and R01 NS041922 to C.J.).

AUTHOR CONTRIBUTIONS

VKP: Acquisition and analysis of data, drafting a significant portion of the manuscript and figures.

JJ: Analysis of data, revising manuscript.

PK: Acquisition and analysis of data, revising manuscript.

AK: Acquisition and analysis of data, revising manuscript.

HTC: Conception and design of study, revising manuscript.

CJ: Conception and design of study, supervising data analysis and statistics, drafting and revising a significant portion of the manuscript.

CONFLICT OF INTEREST

Nothing to report.

ORCID

Jeong-Won Jeong <https://orcid.org/0000-0003-4498-0939>

Csaba Juhász <https://orcid.org/0000-0002-5067-5554>

REFERENCES

- Archambaud, F., Boullieret, V., Hertz-Pannier, L., Chaumet-Riffaud, P., Rodrigo, S., Dulac, O., ... Chiron, C. (2013). Optimizing statistical parametric mapping analysis of 18F-FDG PET in children. *EJNMMI Research*, 3, 2. <https://doi.org/10.1186/2191-219x-3-2>
- Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *NeuroImage*, 38, 95–113. <https://doi.org/10.1016/j.neuroimage.2007.07.007>
- Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society: Series B*, 57, 289–300.
- Chugani, H. T., & Phelps, M. E. (1986). Maturational changes in cerebral function in infants determined by ¹⁸F-FDG positron emission tomography. *Science*, 231, 840–843.
- Chugani, H. T., Phelps, M. E., & Mazziotta, J. C. (1987). Positron emission tomography study of human brain functional development. *Annals of Neurology*, 22, 487–497. <https://doi.org/10.1002/ana.410220408>
- Cohen, P., Cohen, J., West, S., & Aiken, L. S. (2003). *Applied multiple regression/correlation analysis for the behavioral sciences* (3rd ed.). Hillsdale, NJ: Lawrence Erlbaum.
- da Silva, E. A., Chugani, D. C., Muzik, O., & Chugani, H. T. (1997). Identification of frontal lobe epileptic foci in children using positron emission tomography. *Epilepsia*, 38, 1198–1208.
- Gaillard, W. D., Kopylev, L., Weinstein, S., Conry, J., Pearl, P. L., Spanaki, M. V., ... Theodore, W. H. (2002). Low incidence of abnormal (18)FDG-PET in children with new-onset partial epilepsy: A prospective study. *Neurology*, 58, 717–722.
- Gaillard, W. D., Weinstein, S., Conry, J., Pearl, P. L., Fazilat, S., Fazilat, S., ... Theodore, W. H. (2007). Prognosis of children with partial epilepsy: MRI and serial ¹⁸F-FDG-PET. *Neurology*, 68, 655–659. <https://doi.org/10.1212/01.wnl.0000255942.25101.8d>
- Gaillard, W. D., White, S., Malow, B., Flamini, R., Weinstein, S., Sato, S., ... Fazilat, S. (1995). FDG-PET in children and adolescents with partial seizures: Role in epilepsy surgery evaluation. *Epilepsy Research*, 20, 77–84.
- Horwitz, B., Amunts, K., Bhattacharyya, R., Patkin, D., Jeffries, K., Zilles, K., & Braun, A. R. (2003). Activation of Broca's area during the production of spoken and signed language: A combined cytoarchitectonic mapping and PET analysis. *Neuropsychologia*, 41, 1868–1876.
- Hua, C., Merchant, T. E., Li, X., Li, Y., & Shulkin, B. L. (2015). Establishing age-associated normative ranges of the cerebral ¹⁸F-FDG uptake ratio in children. *Journal of Nuclear Medicine*, 56, 575–579. <https://doi.org/10.2967/jnumed.114.146993>
- Ivančević, V., Alavi, A., Souder, E., Mozley, P. D., Gur, R. E., Bénard, F., & Munz, D. L. (2000). Regional cerebral glucose metabolism in healthy volunteers determined by fluorodeoxyglucose positron emission tomography: Appearance and variance in the transaxial, coronal, and sagittal planes. *Clinical Nuclear Medicine*, 25, 596–602.
- Jeong, J. W., Asano, E., Kumar Pilli, V., Nakai, Y., Chugani, H. T., & Juhasz, C. (2017). Objective 3D surface evaluation of intracranial electrophysiologic correlates of cerebral glucose metabolic abnormalities in children with focal epilepsy. *Human Brain Mapping*, 38, 3098–3112. <https://doi.org/10.1002/hbm.23577>
- Kakimoto, A., Ito, S., Okada, H., Nishizawa, S., Minoshima, S., & Ouchi, Y. (2016). Age-related sex-specific changes in brain metabolism and morphology. *Journal of Nuclear Medicine*, 57, 221–225. <https://doi.org/10.2967/jnumed.115.166439>
- Kang, E., Lee, D. S., Kang, H., Lee, J. S., Oh, S. H., Lee, M. C., & Kim, C. S. (2004). Age-associated changes of cerebral glucose metabolic activity in both male and female deaf children: Parametric analysis using objective volume of interest and voxel-based mapping. *NeuroImage*, 22, 1543–1553. <https://doi.org/10.1016/j.neuroimage.2004.04.010>
- Kim, I. J., Kim, S. J., & Kim, Y. K. (2009). Age- and sex-associated changes in cerebral glucose metabolism in normal healthy subjects: Statistical parametric mapping analysis of F-18 fluorodeoxyglucose brain positron emission tomography. *Acta Radiologica*, 50, 1169–1174. <https://doi.org/10.3109/02841850903258058>
- Kinnala, A., Suhonen-Polvi, H., Aarimaa, T., Kero, P., Korvenranta, H., Ruotsalainen, U., ... Wegelius, U. (1996). Cerebral metabolic rate for glucose during the first six months of life: An FDG positron emission tomography study. *Archives of Disease in Childhood. Fetal and Neonatal Edition*, 74, F153–F157.
- Kochunov, P., Ramage, A. E., Lancaster, J. L., Robin, D. A., Narayana, S., Coyle, T., ... Fox, P. (2009). Loss of cerebral white matter structural integrity tracks the gray matter metabolic decline in normal aging. *NeuroImage*, 45, 17–28. <https://doi.org/10.1016/j.neuroimage.2008.11.010>
- Kong, X. Z., Mathias, S. R., Guadalupe, T., Glahn, D. C., Franke, B., Crivello, F., ... ENIGMA Laterality Working Group. (2018). Mapping cortical brain asymmetry in 17,141 healthy individuals worldwide via the ENIGMA consortium. *Proceedings of the National Academy of Sciences of the United States of America*, 115, E5154–E5163. <https://doi.org/10.1073/pnas.1718418115>
- Kumar, A., Juhasz, C., Asano, E., Sood, S., Muzik, O., & Chugani, H. T. (2010). Objective detection of epileptic foci by 18F-FDG PET in children undergoing epilepsy surgery. *Journal of Nuclear Medicine*, 51, 1901–1907. <https://doi.org/10.2967/jnumed.110.075390>
- London, K., & Howman-Giles, R. (2015). Voxel-based analysis of normal cerebral [¹⁸F]FDG uptake during childhood using statistical parametric mapping. *NeuroImage*, 106, 264–271. <https://doi.org/10.1016/j.neuroimage.2014.11.047>
- Luders, E., Narr, K. L., Thompson, P. M., Rex, D. E., Jancke, L., & Toga, A. W. (2006). Hemispheric asymmetries in cortical thickness. *Cerebral Cortex*, 16, 1232–1238. <https://doi.org/10.1093/cercor/bhj064>
- Murphy, D. G., DeCarli, C., McIntosh, A. R., Daly, E., Mentis, M. J., Pietrini, P., ... Rapoport, S. I. (1996). Sex differences in human brain morphometry and metabolism: An in vivo quantitative magnetic resonance imaging and positron emission tomography study on the effect of aging. *Archives of General Psychiatry*, 53, 585–594.
- Muzik, O., Chugani, D. C., Shen, C., da Silva, E. A., Shah, J., Shah, A., ... Chugani, H. T. (1998). Objective method for localization of cortical asymmetries using positron emission tomography to aid surgical resection of epileptic foci. *Computer Aided Surgery*, 3, 74–82. [https://doi.org/10.1002/\(sici\)1097-0150\(1998\)3:2<74::aid-igs4>3.0.co;2-h](https://doi.org/10.1002/(sici)1097-0150(1998)3:2<74::aid-igs4>3.0.co;2-h)
- Muzik, O., Janisse, J., Ager, J., Shen, C., Chugani, D. C., & Chugani, H. T. (1999). A mathematical model for the analysis of cross-sectional brain glucose metabolism data in children. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 23, 589–600.
- Pardoe, H. R., Berg, A. T., & Jackson, G. D. (2013). Sodium valproate use is associated with reduced parietal lobe thickness and brain volume. *Neurology*, 80, 1895–1900. <https://doi.org/10.1212/WNL.0b013e318292a2e5>
- Park, H. J., Lee, J. D., Chun, J. W., Seok, J. H., Yun, M., Oh, M. K., & Kim, J. J. (2006). Cortical surface-based analysis of 18F-FDG PET: Measured metabolic abnormalities in schizophrenia are affected by cortical structural abnormalities. *NeuroImage*, 31, 1434–1444. <https://doi.org/10.1016/j.neuroimage.2006.02.001>
- Plessen, K. J., Hugdahl, K., Bansal, R., Hao, X., & Peterson, B. S. (2014). Sex, age, and cognitive correlates of asymmetries in thickness of the cortical mantle across the life span. *The Journal of Neuroscience*, 34, 6294–6302. <https://doi.org/10.1523/jneurosci.3692-13.2014>
- Rajagopalan, V., & Pioro, E. P. (2015). Comparing brain structural MRI and metabolic FDG-PET changes in patients with ALS-FTD: 'the chicken or the egg?' question. *Journal of Neurology, Neurosurgery, and Psychiatry*, 86, 952–958. <https://doi.org/10.1136/jnnp-2014-308239>
- Rutten, G. J., van Rijen, P. C., van Veelen, C. W., & Ramsey, N. F. (1999). Language area localization with three-dimensional functional magnetic resonance imaging matches intracal electrostimulation in Broca's area. *Annals of Neurology*, 46, 405–408.

- Shan, Z. Y., Leiker, A. J., Onar-Thomas, A., Li, Y., Feng, T., Reddick, W. E., ... Shulkin, B. L. (2014). Cerebral glucose metabolism on positron emission tomography of children. *Human Brain Mapping*, 35, 2297–2309. <https://doi.org/10.1002/hbm.22328>
- Shaw, P., Lalonde, F., Lepage, C., Rabin, C., Eckstrand, K., Sharp, W., & Rapoport, J. (2009). Development of cortical asymmetry in typically developing children and its disruption in attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*, 66, 888–896. <https://doi.org/10.1001/archgenpsychiatry.2009.103>
- Sood, S., & Chugani, H. T. (2006). Functional neuroimaging in the preoperative evaluation of children with drug-resistant epilepsy. *Child's Nervous System*, 22, 810–820. <https://doi.org/10.1007/s00381-006-0137-0>
- Van Bogaert, P., Wikler, D., Damhaut, P., Szliwowski, H. B., & Goldman, S. (1998). Regional changes in glucose metabolism during brain development from the age of 6 years. *NeuroImage*, 8, 62–68. <https://doi.org/10.1006/nimg.1998.0346>
- Wang, G. J., Volkow, N. D., Wolf, A. P., Brodie, J. D., & Hitzemann, R. J. (1994). Intersubject variability of brain glucose metabolic measurements in young normal males. *Journal of Nuclear Medicine*, 35, 1457–1466.
- Widjaja, E., Mahmoodabadi, S. Z., Snead, O. C., Almeshdar, A., & Smith, M. L. (2011). Widespread cortical thinning in children with frontal lobe epilepsy. *Epilepsia*, 52, 1685–1691. <https://doi.org/10.1111/j.1528-1167.2011.03085.x>
- Widjaja, E., Zarei Mahmoodabadi, S., Go, C., Raybaud, C., Chuang, S., Snead, O. C., & Smith, M. L. (2012). Reduced cortical thickness in children with new-onset seizures. *AJNR. American Journal of Neuroradiology*, 33, 673–677. <https://doi.org/10.3174/ajnr.A2982>
- Zhou, D., Lebel, C., Evans, A., & Beaulieu, C. (2013). Cortical thickness asymmetry from childhood to older adulthood. *NeuroImage*, 83, 66–74. <https://doi.org/10.1016/j.neuroimage.2013.06.073>

How to cite this article: Pilli VK, Jeong J-W, Konka P, Kumar A, Chugani HT, Juhász C. Objective PET study of glucose metabolism asymmetries in children with epilepsy: Implications for normal brain development. *Hum Brain Mapp*. 2019; 40:53–64. <https://doi.org/10.1002/hbm.24354>