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Assessment of Brain Damage and Plasticity in the Visual System Due to Early Occipital Lesion: Comparison of FDG-PET with Diffusion MRI Tractography

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Abstract

Purpose—To determine the relation between glucose metabolic changes of the primary visual cortex, structural abnormalities of the corresponding visual tracts, and visual symptoms in children with Sturge-Weber syndrome (SWS).

Materials and Methods—In 10 children with unilateral SWS (ages 1.5–5.5 years), a region-of-interest analysis was applied in the bilateral medial occipital cortex on positron emission tomography (PET) and used to track diffusion-weighted imaging (DWI) streamlines corresponding to the central visual pathway. Normalized streamline volumes of individual SWS patients were compared with values from age-matched control groups as well as correlated with normalized glucose uptakes and visual field deficit.

Results—Lower glucose uptake and lower corresponding streamline volumes were detected in the affected occipital lobe in 9/10 patients, as compared to the contralateral side. Seven of these 9 patients had visual field deficit and normal or decreased streamline volumes on the unaffected side. The two other children had no visual symptoms and showed high contralateral visual streamline volumes. There was a positive correlation between the normalized ratios on DWI and PET, indicating that lower glucose metabolism was associated with lower streamline volume in the affected hemisphere ($R = 0.70$, $P = 0.024$).

Conclusion—We demonstrated that 18F-fluorodeoxyglucose (FDG)-PET combined with DWI tractography can detect both brain damage on the side of the lesion and contralateral plasticity in children with early occipital lesions.

Keywords

Sturge-Weber Syndrome; DWI tractography; FDG-PET

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STURGE-WEBER SYNDROME (SWS) is a rare disorder, affecting one in 20,000–50,000 people, and is associated with a somatic gene mutation (1) and characterized by a facial port-wine birthmark and leptomeningeal vascular malformation (2). Children with SWS can have a variety of neurologic problems, including motor deficit, visual field impairment, cognitive decline, and seizures. The first neurological symptoms (most commonly seizures) often start during the first year of life and show a highly variable clinical course (3). Cerebral abnormalities in SWS affect only one hemisphere in 85% of the cases, with the most common location of the leptomeningeal angioma in the posterior cerebral cortex involving the occipital lobe (2,3).

Clinical magnetic resonance imaging (MRI) can detect brain venous vascular abnormalities as well as tissue damage (atrophy, calcification) underlying the angioma, while 2-deoxy-2[¹⁸F]fluoro-D-glucose positron emission tomography (FDG-PET, typically reserved for evaluation for epilepsy surgery) often shows cortical glucose hypo-metabolism extending beyond the structural brain abnormalities (4–6).

SWS with unilateral hemispheric involvement allows for the study of early focal brain damage and injury-induced brain plasticity in an etiologically homogeneous patient population. Early postnatal brain injury can induce effective reorganizational processes in the developing human brain, which attempts to compensate for the functional effects of injury (7–9). Imaging can be used to study remote functional effects of focal brain lesions in children. For example, in an activation ¹⁵O-water PET study of children with SWS affecting one hemisphere, interhemispheric reorganization of language functions was found despite some retained functions in the affected hemisphere (10). Also, some children with early-onset severe unihemispheric damage due to SWS show relatively preserved cognitive functions (11,12). These observations suggest that early deterioration in the affected hemisphere may induce effective reorganizational processes, which can lead to a transfer of many functions to nonaffected cortical regions either within the ipsilateral or in the contralateral hemisphere. Increased glucose metabolism detected by PET, remote from an early cerebral lesion, may be a hallmark of such functional reorganization (7,13). In our previous PET study, we observed increased glucose metabolism in the unaffected occipital cortex contralateral to the severely damaged occipital lobe of SWS children (14). However, the mechanisms and functional correlates of this observation remained uncertain.

Diffusion-weighted imaging (DWI) streamline tractography is a noninvasive tool to detect structural and architectural change in specific cerebral fibers by measuring the dephasing of spins of protons in the presence of a spatially varying magnetic field (15–18). In the present study, we combined DWI streamline tractography with FDG-PET in children with unilateral SWS. We hypothesized that decreased occipital glucose metabolism will be associated with decreased visual streamline volume on the affected side. We also hypothesized that high glucose metabolism in the contralateral occipital (visual) cortex may be associated with high DWI streamline volume of the corresponding visual pathway. Finally, we evaluated the clinical correlates of the imaging abnormalities in the visual system, both ipsi- and contralateral to the lesion.

The overall purpose of the study was to determine the relation between glucose metabolic changes of the primary visual cortex, structural abnormalities of the corresponding visual tracts, and visual symptoms in these children.

MATERIALS AND METHODS

Subjects

From our database of 70 children (age 3 months to 13 years; 41 girls, 29 boys) with SWS, who participated in a prospective, longitudinal neuroimaging study, we selected 10 patients (Table 1), who fulfilled the following inclusion criteria: 1) Unilateral SWS diagnosed by the presence of a port-wine birthmark and leptomeningeal angioma in the posterior brain regions, including the occipital lobe, detected by contrast-enhanced MRI; 2) Age between 1–6 years; 3) DWI and interictal FDG-PET performed within 24 hours. All patients underwent a neurological evaluation at the time of the scans to assess visual function (including visual field deficit) along with other neurological symptoms by a board-certified pediatric neurologist (H.T.C.) with more than 25 years of experience in the clinical management of children with SWS; in six children, neurological examination was repeated at least 1 year later. All 10 children with SWS had a history of seizures, but only one child (#3 in Table 1) had glaucoma. In three of the 10 children (#2, 3, and 6 in Table 1), DWI studies and neurological examination were repeated 1 (#2 and 3) or 2 years later (#6) to assess changes in microstructural abnormalities and corresponding visual field deficits.

For each child with SWS, one of three age-matched groups were selected as controls (group 1: five 2-year-old children, group 2: three 3-year-old children, and group 3: five 4-year-old children) obtained from our DWI database of children who underwent MRI due to history of seizures. None of the control children had structural lesions on MRI (as determined by a pediatric neuroradiologist), and none of them had significant developmental delay based on their clinical reports.

The Human Investigations Committee (HIC) granted permission for the longitudinal clinical and neuroimaging study and multimodal comparisons of the children with Sturge-Weber syndrome and parents signed an informed consent form. We also had permission from the HIC to use the clinically acquired MRI scans (from children with epilepsy) after deidentification.

Data Acquisition

For children with SWS, a Siemens MAGNETOM Trio 3T scanner (Siemens Medical Solutions, Erlangen, Germany) with a standard head array coil was used to acquire diffusion-weighted images at repetition time (TR) = 6,600 msec, echo time (TE) = 97 msec, field of view (FOV) = 256 mm, matrix size = 128 × 128 (nominal resolution = 2 mm), slice thickness = 2 mm, and zero gap covering the whole brain using 64 isotropic gradient directions with $b = 1000 \text{ s/mm}^2$, one $b = 0$ acquisition, and number of excitations (NEX) = 2. All children had additional native and postcontrast MRI sequences to establish the diagnosis of SWS and to study the extent of brain involvement. Also, all SWS children underwent interictal FDG-PET scanning using an EXACT/HR PET scanner (CTI/Siemens, Hoffman

Estates, IL), which provides simultaneous acquisition of 47 contiguous transaxial images (nominal resolution = 1.76 mm) with slice thickness of 3.13 mm (28). Intravenous injection of 5.29 MBq/kg of FDG was followed by a 30-minute uptake period. During the scanning phase scalp EEG was monitored. Forty minutes postinjection, a static 20-minute emission scan was acquired parallel to the canthomeatal plane. Sedation was induced by pentobarbital (3 mg/kg) and maintained by fentanyl (1 µg/kg), applied only during the PET/MRI scanning (not during tracer uptake).

For controls, MRI scans were performed on a 3T GE-Signa scanner (GE Healthcare, Milwaukee, WI) equipped with an 8-channel head coil and ASSET. DWI was acquired with a multislice single-shot diffusion-weighted echo-planar-imaging (EPI) sequence at TR = 12,500 msec, TE = 88.7 msec, FOV = 240 mm, 128×128 acquisition matrix (nominal resolution = 1.89 mm), contiguous 3 mm thickness in order to cover entire axial slices of whole brain using 55 isotropic gradient directions with $b = 1000 \text{ s/mm}^2$, one $b = 0$ acquisition, and NEX = 1. Scanning time for the acquisition was about 12 minutes using double refocusing pulse sequence to reduce eddy current artifacts.

Data Analysis

Localization of Regions of Interest for PET and DWI Tractography—A block diagram illustrating the procedure to determine two regions of interest (ROIs) for multimodal comparison is presented in Fig. 1. First, an ROI including the unaffected (contralateral to angioma) medial occipital cortex and occipital pole, showing prominent uptake on PET in the visual cortex, was drawn on the native FDG-PET images of each individual patient with SWS. A conventional SPM-DARTEL approach (19) was used to construct a pediatric FDG-PET template using 10 normal FDG-PET images obtained from focal epilepsy children below the ages of 3 years and finding an optimal deformation field, $M_1(x,y,z)$, to spatially normalize each FDG-PET image to the pediatric FDG-PET template. The occipital ROI drawn in the unaffected side (ROI_c: contralateral ROI) was then transferred to MNI space and flipped vertically to create a corresponding ROI in the affected hemisphere (ROI_i: ipsilateral ROI). The location of the ROI_i was appropriately adjusted to fit onto affected occipital cortex with atrophy. Finally, the resulting ROIs were moved onto the FDG-PET image by applying the inverse mapping of $M_1(x,y,z)$ to evaluate glucose uptake in both ROIs.

Similarly, a nonlinear deformation field, $M_2(x,y,z)$ was obtained between a b_0 image of the patient and a pediatric b_0 template constructed from b_0 images of a corresponding control group using a conventional SPM-DARTEL approach (19). The inverse field of $M_2(x,y,z)$ was directly applied to move a set of ROIs (ROI_c and ROI_i) into a b_0 image of the subject. The resulting set was finally used to seed individual streamlines in the following DWI tractography procedure.

To obtain age-appropriate control values for each patient, we repeated the above procedure to locate two ROIs of each individual patient into age-matched control subjects, where the two occipital ROIs (left and right) of each patient were first determined in two different MNI spaces, one for PET and another for DWI b_0 . These ROIs were then moved into native space of individual control subjects via M_1 (for PET) and M_2 (for DWI), which were

determined between the images of each control subject and standard MNI templates. Finally, the streamline volumes from the left and right ROIs (which showed no consistent asymmetry) were averaged for comparison with the values of the SWS patients (see Table 1).

DWI Tractography to Detect Visual Pathways in Unaffected and Affected Hemisphere

Independent component analysis with a ball-and-stick model (“ICA +BSM”) tractography (20,21) was used to detect the central visual pathway in both hemispheres where each visual cortical ROI obtained (Fig. 1) was used as a seeding region, and ipsilateral thalamus was applied as a terminating region. For the streamline tractography, maximal number of crossing stick components = 3, step size = 0.2 voxel width, angle threshold = 60°, and the fraction of individual stick component >0.05 were applied. Propagation direction was calculated by applying trilinear interpolation on the stick orientations provided from 26 nearby voxels of the current point. For each nearby voxel, only the stick orientation that had the smallest turning angle was considered for interpolation. In order to smoothen the streamlines, each subsequent direction was determined by equal weighting of the previous moving direction and incoming direction.

For each hemisphere, a streamline visitation map was created by counting the number of streamlines passing per voxel. Voxels having more than 1 visit were assumed to belong to the visual pathway. Streamline volume was measured by the total volume of all voxels belonging to the pathway.

Correlation Between PET and DWI Tractography Data—To investigate whether visual cortical glucose metabolism is related to streamline volume in the central visual pathway of children with SWS, we correlated glucose metabolism asymmetry with streamline volume asymmetry across the hemispheres. The lateralization index (LI) of the total streamline volume and glucose uptake was calculated from a set of two regions, ROI_c: unaffected side and ROI_i: affected side, as shown on Fig. 1, using the ratio of (ROI_c+ROI_i) and (ROI_c-ROI_i). Furthermore, in order to quantify the degree of hypo- or hypermetabolism in ROI_c and ROI_i, a normalized glucose uptake ratio value was calculated by dividing the value of each occipital cortical ROI to the value of normal cortex measured in the frontal lobe of unaffected side (ie, baseline). Similar volume ratio values were calculated by normalizing the streamline volume of each ROI to total hemispheric streamline volume of the unaffected side.

Statistical Analysis

Pearson correlations were performed to study the relation between glucose uptake and corresponding streamline volumes. $P < 0.05$ was considered significant at two-tailed probability (alpha = 0.05).

RESULTS

Lower glucose uptake on PET and lower corresponding streamline volumes on DWI were detected in the affected occipital lobe (ROI_i), as compared to the contralateral side (ROI_c), in all but one SWS child; the only exception was patient #8 (with no visual symptoms), who

showed almost equal values bilaterally on both modalities (Table 1). In one child (patient #3), with the lowest occipital glucose uptake on PET (uptake ratio 0.491) ipsilateral to the lesion, no streamlines could be identified by DWI on the affected side. She also had the lowest streamline volume in the contralateral occipital lobe (volume ratio: 0.006; control mean: 0.020), which showed no angioma (Fig. 2a). This child showed the most severe visual symptoms, with left hemianopia and also severe glaucoma affecting vision in her right eye. In contrast, two children (patients #7 and #10) showed very prominent FDG uptake and/or normalized streamline volume above control mean values in the contralateral occipital lobe (Table 1, Fig. 2b,c). This increase was most striking (>2 SD above control mean) in the contralateral visual fibers of patient #10, who had no visual field deficit at the time of the scans or at 1-year follow-up, at age 6.5 years. Patient #6 (3.3 years old), with streamline volumes similar to age-matched control means on the unaffected side had a possible quadrant anopia. Five children (#1, 2, 4, 5, and 9) with definite hemianopia had low streamline volumes in the affected occipital lobe and higher, but still below the normal mean, on the unaffected side (Table 1).

On longitudinal MRI studies performed in three children with variable severity of visual deficit, patient #2 showed a clear progression suggested by the loss of visual streamlines on the affected side, while the streamline volume ratio was stable in the unaffected occipital lobe (Fig. 3). Patient #3, with the most severe visual symptoms (see above) and no detectable streamlines on the affected side, a slight interval increase but still subnormal values were seen on the unaffected side. The values of patient #6 (quadrant hemianopia) were on the low end of the normal range at baseline on the lesion side and closely followed the age-matched control values (ie, a decrease between age 3 and 4 years) in the unaffected visual pathway during follow-up (Fig. 3).

In cross-modal (DW-MRI/FDG-PET) analysis, a positive correlation was observed in the LI values of corresponding ROIs (Fig. 4a; $R = 0.64$, $P = 0.046$). Also, there was a positive significant correlation between the normalized ratios of ROI_c and ROI_i in PET and DWI. Lower metabolism was associated with lower DWI streamline volume on the affected side ($R = 0.70$, $P = 0.024$; Fig. 4b, left panel). Only a nonsignificant trend was observed in the unaffected occipital lobe of the SWS children (right panel of Fig. 4b; $R = 0.20$, $P = 0.56$).

DISCUSSION

This is a proof-of-concept multimodal imaging study demonstrating abnormalities of occipital glucose metabolism and the corresponding visual pathway in young SWS children with occipital lobe lesion on one side (which affects visual pathways at an early age). Despite the limited number of patients, we found a correlation between abnormalities of cortical metabolism and corresponding subcortical visual pathways on the affected side. Importantly, we also found evidence for high streamline volume in the contralateral (unaffected) visual pathway, with or without prominent cortical glucose uptake, in two children. Interestingly, these two children showed no obvious clinical signs of a visual field deficit at the time of the scans or 1 year later, despite low ipsilateral values suggesting visual pathway damage in the affected occipital lobe. On the other hand, five other children with low streamline values on the affected side showed no increases in the contralateral pathway,

and all five had hemianopia. This suggests that structural and functional reorganization of the central visual system, using contralateral pathways, could result in (or contribute to) a clinically detectable preservation of visual functions in young children with occipital brain damage, while lack of such reorganization is associated with permanent hemifield deficit.

Visual plasticity in humans is less commonly reported than plasticity of the motor or language systems, but at least a few cases have been described where functional reorganization or recovery was documented after early occipital lesions (22,23). Indeed, limited functional MRI (fMRI) studies demonstrated hemifield function to be shifted from the damaged occipital lobe to the ipsilateral temporal and parietal lobes (23). In another study, an 11-year-old girl with SWS who learned to read after complete surgical resection of her left occipital lobe showed fMRI evidence of a left-to-right shift of the visual (but not verbal) component of reading (24). In our cases, both the PET and DWI results support that the contralateral (nonlesional) occipital lobe participated in reorganization of visual functions. Early, severe occipital damage, demonstrated by imaging, likely facilitated these compensatory changes. The high streamline volume in the unaffected hemisphere provides novel imaging evidence for an apparent structural reorganization of the central visual tract, which is a novel finding.

In the only child with both hemianopia and decreased vision due to glaucoma in the affected eye, bilateral (although asymmetric) damage in the central visual pathway was an unexpected finding considering the lack of SWS brain involvement in the left hemisphere of this child on conventional MRI. One can speculate that the presence of glaucoma, affecting her vision early, may have interfered with the compensatory changes that could have otherwise occurred. Early, severe visual deprivation may elicit cross-modal reorganization in intact visual areas (25), but the combination of both central and peripheral visual pathology may preclude such reorganization processes.

The cross-modal correlations showed a strong relation between severity of occipital cortical damage (evaluated by PET) and damage of the underlying central visual pathway (on DWI) in the affected hemisphere. This suggests that DWI alone could be useful to assess the severity of early occipital damage and the PET findings add little additional information. On the other hand, the lack of clear cross-modal correlation on the unaffected side may indicate that metabolic and structural abnormalities and/or reorganizational changes may not always occur in the same patient or may occur at different times during brain development. Thus, in studies of lesion-induced plasticity, DWI and PET may provide complementary information. Altogether, the presented results demonstrate that advanced imaging using DWI tractography may be useful to evaluate the damage, progression, and possible reorganization of the visual system in children affected by early occipital damage due to SWS and possibly other etiologies affecting the central visual system. This could be instrumental to advise parents regarding potential visual deficits (which are difficult to test in the very young), and perhaps predict potential visual consequences of hemi-spherectomy or posterior resection in those who undergo epilepsy surgery due to intractable seizures.

The present study has several limitations and warrants further confirmation in larger patient samples. A post-hoc power analysis showed that the sample size of 96 would reveal a

statistically significant correlation between FDG uptake ratio and streamline volume ratio in the unaffected side, if we assume that $R = 0.20$ remained in the larger population. The lack of an objective visual field measure, due to the young age of most subjects, prevented us from performing further, detailed correlations between the imaging measures and severity in visual deficits. Another limitation is that the comparisons were made with control subjects who were scanned due to focal epilepsy. However, we considered this patient group to be a reasonable control population, because these children had normal structural MRI (and no history of any visual problems), and all children in both groups had epilepsy. Therefore, the observed differences can be attributed to SWS lesion affecting the posterior hemisphere, rather than epilepsy. Although the two patient populations were scanned on different MRI scanners, our analyses relied on normalized values and asymmetries (rather than absolute values of streamline volumes), which have been reported to diminish interindividual variations and age-related changes in MR volumetric studies (26,27). Age effects were also accounted for by choosing age-matched control groups for each SWS patient for individual comparisons. Finally, our analysis was confined to the central visual pathway, with streamline tracking initiated from the visual occipital cortex. Therefore, additional reorganizational changes in extra-visual systems could not be addressed, but can be assessed in future studies.

In addition, spatial normalization of brain MRI, particularly in the presence of pathological tissue, is significantly challenging due to atypically disrupted anatomy (atrophy) and tissue contrast (partial volume effect). Although the accuracy of the SPM DARTEL was successfully validated to normalize PET and MRI for voxel-wise analysis (28,29), this normalization cannot guarantee perfect registration over the whole brain. In fact, we observed that the deformation was quite accurate at deep structures such as major association tracts, but not as accurate in subcortical, peripheral regions where atrophy and partial volume effect likely exist. To overcome this limitation, future studies should incorporate more sophisticated schemes of spatial normalization utilizing either atlas-landmark based multichannel deformation algorithms (30,31) or surface-based registration methods using fast diffeomorphic landmark-free registration (32).

In conclusion, the present study demonstrates that FDG-PET and DWI tractography can be used to investigate brain damage and plasticity in children with occipital damage, and the findings can provide clinically meaningful, quantitative data on the visual system. These results support that increased streamline volume in DWI tractography may be a hallmark of a clinically meaningful structural reorganization associated with increased occipital glucose uptake. This approach can be used in future studies of older children and adults to further establish the clinical relevance of these visual pathway abnormalities.

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Figure 1.

The procedure to define two ROIs, including the medial occipital cortex and occipital pole, on PET and DWI, ROI_c on the contralateral (unaffected) side and ROI_i on the ipsilateral (affected) side. Two deformation fields, M_1 and M_2 , were obtained using the SPM-DARTEL approach in order to define voxel-wise mapping fields between native space and standard MNI space where M_1 and M_2 represent different nonlinear deformation functions for PET and DWI, respectively. The inverse functions of these fields, M_1^{-1} and M_2^{-1} , were utilized to define two ROIs on PET and DWI in native space.

Figure 2.

Representative patients showing significant metabolic and/or pathway abnormalities in the central visual system. **a:** Patient #3 (Table 1), with the lowest occipital glucose uptake on PET (uptake ratio 0.491) and no visual pathway streamlines identified by DWI on the affected right side. The contralateral streamline volume was also low; this child had severe visual symptoms. **b:** An older child (patient #7, age 3.9 years) showed very prominent FDG uptake and high (about 1 SD above normal average) streamline volume in the occipital lobe unaffected by SWS (marked by “+”). **c:** The oldest child (patient #10, age 5.5 years) showed moderate FDG uptake but very high streamline volume (>2 SD above normal average) in the occipital lobe unaffected by SWS (marked by “+”), suggesting reorganization. These latter two children had no evidence of visual field deficit. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 3.

Longitudinal changes in streamline volume ratios obtained from three children with SWS, #2, #3, and #6 with variable visual deficits (see Table 1). Average values (and SDs) of age-matched normal controls are also displayed for comparison (in black). The data demonstrate a clear progression on the affected side in patient #2 (blue line) during the 1-year follow-up period. This patient had a left visual field deficit at follow-up. Patient #3 (severe visual field defect and unilateral vision loss due to glaucoma) showed no detectable fibers at either timepoint; while patient #6 (green; possible quadrant anopia) had the volume ratios in the low normal range at baseline which remained stable at follow-up. On the unaffected side, normalized volume ratios followed the normal curve in this patient, while the other two patients showed values below the normal average during follow-up, although a mild/moderate increase (but not normalization) was seen in both. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 4.

Positive correlations between glucose uptake and streamline volume obtained from visual areas of the children with SWS. **a:** Positive correlation between lateralization index of normalized FDG uptake and streamline volume ($R = 0.64$, $P = 0.046$). **b:** Normalized ratios of FDG uptake and streamline volume in ROI_c and ROI_i. The correlation was particularly strong, despite the small numbers, on the affected side ($R = 0.70$, $P = 0.024$).

Table 1

Clinical Data

No.	Age (years)	Affected side and lobes	Visual field deficit	FDG-PET		DWI MRI normalized volumes			
				Uptake ratio		SWS patients		Controls	
				ROI _c	ROI _i	ROI _c	ROI _i	ROI _c	ROI _i
1	1.5	Left TPO	Right field (at age 2.5 years)	0.981	0.867	0.010	0.004	0.020±0.006	
2	1.6	Right OTP (F)	Left field (at age 2.6 years)	1.274	1.007	0.015	0.012		
3	1.8	Right OTP (F)	Left field + impaired right eye vision due to glaucoma (at age 2.8 years)	1.176	0.491	0.006	0.000		
4	2.0	Left OT (P)	Right field (at age 2.0 years)	1.199	1.023	0.014	0.010		
5	2.5	Left O (TP)	Right field (at age 2.5 years)	1.078	0.902	0.019	0.018	0.022±0.004	
6	3.3	Right OP	Possible left lower quadrant (at age 5.3 years)	1.211	1.200	0.024	0.014		
7	3.9	Left OTP	None or minimal (at age 4.9 years)	1.293	0.708	0.021	0.008	0.014±0.007	
8	4.7	Right TPO	None (at age 4.7 years)	1.053	1.058	0.011	0.010		
9	5	Left FTPO	Right field (at age 5 years)	1.120	0.536	0.010	0.008		
10	5.5	Left TPO	None (age 6.5 years)	1.053	0.591	0.031	0.002		

Normalized glucose PET uptake in the visual cortex (normalized to normal frontal cortex) and corresponding DWI ratio, normalized to hemispheric white matter volume of the five patients with SWS. ROI_c and ROI_i indicate the visual cortex region of interest defined in the unaffected side and affected side, respectively (and on the corresponding side in the control group). For each patient, control mean ±one standard deviation of DWI ratios were obtained from one of three age-matched control groups who had epilepsy but normal clinical MRI. O = occipital, P = parietal, T = temporal, F = frontal (mild involvement in parentheses).