



Quantitative magnetic resonance imaging evidence for altered structural remodeling of the temporal lobe in West syndrome

*†‡Tangunu Fosi, §Carlton Chu, ¶Wui Khean Chong, #Chris Clark, *‡**††Rod C. Scott, †‡Stewart Boyd, ‡‡Michelle De Haan, and *‡**Brian Neville

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SUMMARY

Objective: To explore the structure–function relation of the temporal lobe in newly diagnosed West syndrome of unknown cause (uWS).

Methods: Quantitative magnetic resonance imaging (three-dimensional [3D] structural MRI and diffusion tensor imaging [DTI]) was analyzed using voxel-based morphometry (VBM) and tract-based spatial statistics (TBSS) in 22 patients and healthy age-matched controls. The electrophysiologic responsiveness of the temporal lobe was measured using the N100 auditory event-related potential (aERP) to a repeated 1,000 Hz tone. Neurocognitive function was assessed using the Bayley Scales of Infant Development, Second Edition (BSID-II). Tests followed first-line treatment with vigabatrin (17 patients) or high-dose oral prednisolone (5 patients).

Results: Total temporal lobe volume was similar in patients and controls. Patients had a smaller temporal stem (TS) ($p < 0.0001$) and planum temporale (PT) ($p = 0.029$) bilaterally. TS width asymmetry with a larger right-sided width in controls was absent in patients ($p = 0.033$). PT asymmetry was present in both groups, being larger on the right ($p = 0.048$). VBM gray matter volume was increased at the left temporal lobe (superior and middle temporal gyri, the peri-rhinal cortex, and medial temporal lobe) ($p < 0.005$, family wise error-corrected). VBM gray matter volume correlated with the duration of infantile spasms (Pearson's $r = -0.630$, $p = 0.009$). DTI metrics did not differ between patients and controls on TBSS. Mean BSID-II scores were lower ($p < 0.001$) and auditory N100 ERP attenuated less in patients than in controls ($p = 0.002$).

Significance: The functional networking and white matter development of the temporal lobe are impaired following infantile spasms. Treatment may promote structural plasticity within the temporal lobe following infantile spasms, manifest as increased gray matter volume on VBM. It remains to be investigated further whether this predicts patients' long-term cognitive difficulties.

KEY WORDS: West syndrome, Temporal lobe, Auditory event-related potential, Quantitative magnetic resonance imaging.



Dr. Tangunu Fosi is a pediatric neurologist and completed a research fellowship in childhood epilepsy at Young Epilepsy in the United Kingdom.

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*Young Epilepsy, Surrey, United Kingdom; †Department of Clinical Neurophysiology, Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom; ‡Neurosciences Unit, University College London Institute of Child Health, London, United Kingdom; §The Functional Imaging Laboratory, University College London, London, United Kingdom; ¶Department of Neuroradiology, Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom; #RCS Unit of Biophysics, University College London Institute of Child Health, London, United Kingdom; **Department of Neurology, Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom; ††Department of Neurological Sciences, University of Vermont, Burlington, Vermont, U.S.A.; and ‡‡Centre for Developmental Cognitive Neurosciences, University College London, London, United Kingdom

The statistical analyses in this work were performed by the corresponding author.

Address correspondence to Tangunu Fosi, UCL Institute of Child Health, 4-5 Long Yard, London WC1N 3LU, U.K. E-mail: sejtfo@ucl.ac.uk

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Early childhood-onset epilepsies are accompanied by behavioral, psychiatric, and cognitive disorders.¹ Epileptic encephalopathy (EE) refers to these outcomes,² but remains without structural or functional substrate despite devastating effects on future development. The most common EE, West syndrome (WS), affects about one in 3,000 live births and presents at around 4–6 months of age with the triad of clustered epileptic spasms, hypsarrhythmic electroencephalography (EEG), and regression. The cause is unknown in 25% (uWS). One half of this class of WS patients shows significant long-term cognitive impairment.³ Because of the absence of lesions, uWS provides a useful model for quantitative magnetic resonance imaging (MRI) study of West syndrome, without the distortions that structural lesions would introduce.

The classical electrographic pattern of WS, hypsarrhythmia, involves all cortical areas⁴ with posterior emphasis.⁵ Hypsarrhythmia evolves to an occipitotemporal sequence of focal discharges.⁶ Its deleterious effect on participating cortical areas has been demonstrated for the occipital lobe.⁷ The possibility of a similar effect on the temporal lobes is suggested by the dramatic loss of auditory and visual responsiveness, decreased vocalization, and regression of social abilities following the onset of infantile spasms.⁸ These are reminiscent of bitemporal impairment.⁹ Functional compromise of the temporal lobe in WS has been further suggested by clinical,^{10,11} auditory event-related potential (aERP),¹² and radionuclide imaging¹³ studies.

The authors considered that functional deficits of the temporal lobe in the setting of WS might reflect its structural alteration. This possibility was investigated with quantitative MRI: three-dimensional (3D) structural morphometry, and diffusion tensor imaging (DTI). Temporal lobe function was measured objectively using scalp voltage changes in response to patterns of auditory stimuli, known as aERPs. Their use for measuring temporal function noninvasively at millisecond resolution is well established.¹⁴

METHODS

Subjects

The joint ethics committee of the University College London Institute of Child Health and Great Ormond Street Hospital (GOSH) approved the study. Parental written informed consent was obtained prior to participation.

Controls

Controls showed age-appropriate development without congenital hearing impairment, chronic otitis media, or other significant health problems at parental interview. Controls came from the community and from university staff. Brain MRI scans were performed in natural sleep following a feed with the infant swaddled (“feed and wrap,” FW) at the first morning scanning session. Imaging was performed

if the infant remained asleep in the MRI scanner tunnel after the initial localizer pulses.

Patients

Cases were recruited prospectively and consecutively from infants younger than 12 months old with newly diagnosed WS referred to a tertiary children’s hospital in England (GOSH). The study did not interfere with normal clinical management. The patients received standard clinical care including history, neurologic examination, clinical investigations, and pharmacologic treatment. Clinical investigations included the following: video-EEG, neuroimaging (epilepsy protocol brain MRI including 3D fast low angle shot magnetic resonance imaging [FLASH] volumetric sequences, plus add-on diffusion tensor imaging for the study), and neurometabolic tests of blood, urine, and cerebrospinal fluid (CSF). This study was limited to patients with infantile spasms and appropriate EEG features whose brain MRI, neurometabolic investigations (blood, urine and cerebrospinal fluid), and karyotype or comparative genome hybridization array did not show abnormality.

The neurologists counseled parents about WS treatments,¹⁵ and commenced patients on treatment after video-EEG confirmation of WS. Treatment was initiated prior to the MRI scan, which was performed as soon as possible. The scan was performed under anesthetist-supervised chloral hydrate sedation, except in patients who already had a brain MRI locally. These patients were scanned at GOSH under FW after parental administration of the child’s anticonvulsant. Infants wore sound-attenuating earplugs. The brain MRI studies were reported by clinical pediatric neuroradiologists.

Measurements

Magnetic resonance imaging

3D-FLASH volumetric images at 1 mm isotropic voxel resolution, and DTI at 2.5 mm isotropic voxel resolution were acquired on a 1.5T Siemens Avanto (Siemens AG, Erlangen, Germany). The 3D data were segmented into gray and white matter using a tissue probability map (TPM) from 2-year-old children.¹⁶ Voxel-based morphometry (VBM) analysis with the SPM5 software (Statistical Parametric Mapping, Wellcome Functional Imaging Laboratory, University College London, London, United Kingdom) used a customized infant brain template.

DTI analysis used tract-based spatial statistics (TBSS; Functional Magnetic Resonance Imaging of the Brain Software Laboratory, University of Oxford, Oxford, United Kingdom; www.fmrib.ox.ac.uk/fsl). The threshold for significance was a family-wise error-corrected p -value < 0.005 . Further details are provided in Data S1.

Electrophysiology

aERPs were recorded during sleep as described in Data S1.

Psychometrics

A clinical neuropsychologist (MDH) performed a standardized assessment of patients' neurodevelopmental abilities with the Bayley Scales of Infant Development, Second Edition (BSID-II).¹⁷

Statistical analysis

The SPSS package (Statistical Package for the Social Sciences for Windows, Version 16.0, SPSS Inc., Chicago, IL, U.S.A.) was used for group patient versus control group repeated-measures analysis of variance (ANOVA) comparisons of manual volumetry. The p-values corrected using the Greenhouse-Geisser procedure are reported. Post hoc linear regression was used to evaluate the relationship between the manual volumetry of the temporal lobe and its electrical activity as assessed using aERP, and the relationship between treatment and MR volumetric data. The criterion for statistical significance was a p-value of <0.05.

RESULTS

Infantile spasms had a median onset of 5 months old (range 4–7 months), with a median treatment lag of 4 weeks (range 2–20 weeks) using vigabatrin (17 patients) or high-dose oral prednisolone (5 patients). All patients had electroclinical remission with cessation of

infantile spasms and resolution of hypsarrhythmia.¹⁸ The median interval to hypsarrhythmia resolving was 22 days (range 4–90 days) from initiating treatment. MRI was successful by sedation (n = 18) or FW (n = 4). aERP testing occurred at a median age of 8 months (range 5–11 months), being a median interval of 2 months (range 0.5–5 months) from initiating treatment. The median interval between spasm onset and ERP was 2.5 months (range 1–7 months). The patient data are summarized in Table 1.

The controls (11 female) had median age 6 months (range 3–12 months). ERP recording was performed in all 22 controls, and MRI in 12, with 3 controls requiring a second scan about a week later because of FW failure. Control details are shown in Table S1.

Magnetic resonance imaging

Voxel-based Morphometry

The MRI acquisition parameters are shown in Table S2. Total gray matter (GM) and white matter (WM) volume were obtained from the modulation step of the VBM pre-processing (Fig. S1). The two groups did not differ in total GM volume (t = 0.505, p = 0.620) or WM volume (t = 0.945, p = 0.355; see Fig. S1, Table 2). WM volume of controls exceeded GM volume (paired t = -14.009, p < 0.0001), whereas patients did not show this difference

Table 1. The patient characteristics

Patient	Sex	Age at ERP (mo.)	Age at spasm onset (mo.)	Rx lag (wks)	Age at Rx start (mo.)	Age at spasm cessation (mo.)	Rx time to spasm cessation (mo.)	Rx
1.	F	9	7	3	7	9	2	STER VGB
2.	F	11	4	8	6	9	3	STER VGB
3.	M	11	6	4	7	9	2	VGB
4.	M	6	5	4	6	6	<1	VGB
5.	F	8	4	8	6	6	<1	VGB
6.	M	7	4	8	6	6	<1	VGB
7.	F	7	6	4	7	7	<1	VGB
8.	M	10	6	4	7	8	1	VGB
9.	M	7	5	3	5	6	1	VGB
10.	M	5	4	4	5	5	<1	VGB
11.	F	9	5	4	6	6	<1	STER
12.	F	10	4	20	9	10	1	VGB VPA
13.	M	6	4	2	4	5	1	VGB
14.	M	8	5	4	6	6	<1	VGB
15.	F	10	7	4	8	8	<1	VGB VPA
16.	M	7	6	2	6	6	<1	VGB
17.	F	7	5	2	6	6	<1	VGB
18.	F	6	4	8	6	6	<1	VGB
19.	F	8	7	2	7	7	<1	VGB
20.	M	11	7	4	8	11	3	STER VGB
21.	F	7	5	2	5	6	<1	VGB
22.	F	8	6	3	7	7	<1	STER

Rx, treatment; VGB, vigabatrin; STER, prednisolone; VPA, sodium valproate; mo., months, wks, weeks.

Correction added on March 24, 2015, after first online publication: The values for Patients 21 and 22 were accidentally omitted before initial online publication.

Table 2. Quantitative MRI data

	Controls Mean (SD)	Patients Mean (SD)	t-test t (two-tailed p-value)
Total intracranial volume (cm ³)	261.4 (55.3)	260.4 (49.7)	0.052 (0.959)
Gray matter volume (cm ³)	81.4 (18.1)	78.2 (15.1)	0.505 (0.620)
White matter volume (cm ³)	89.2 (19.8)	81.9 (22.5)	0.945 (0.355)
Temporal lobe volume left (cm ³)	13.9 (5.0)	10.9 (4.2)	1.624 (0.120)
Temporal lobe volume right (cm ³)	14.7 (5.5)	12.1 (6.0)	1.166 (0.256)
Planum temporale left (cm)	19.1 (3.8)	15.9 (4.2)	1.985 (0.059)
Planum temporale right (cm)	21.3 (2.9)	17.2 (5.7)	2.361 (0.028)
Temporal stem left (cm)	9.4 (2.4)	7.3 (2.0)	2.289 (0.033)
Temporal stem right (cm)	11.6 (1.9)	7.0 (2.4)	5.373 (<0.0001)

Statistically significant values shown in bold.

(paired $t = -0.881$, $p = 0.388$, although the interaction term between the two groups was not significant; see Fig. S2).

VBM analysis was performed at a spatial threshold of 8 mm. The GM volume in the superior and middle temporal gyri, the peri-rhinal cortex, and the medial temporal lobe was increased compared to controls (family-wise error $p < 0.005$). This had a left emphasis (Fig. 1). VBM did not find areas of higher GM volume in controls compared to uWS patients. A search for bilateral changes in the same lobe was performed by expanding the spatial threshold to 12 mm. Only the temporal lobe showed bilateral GM increase (Fig. S3).

Manual volumetry of the temporal lobe

Hemispheric asymmetry of the temporal lobe in infancy. The temporal lobe did not show a statistically significant right-left volume difference in either patients or controls (within-subject effect $F = 1.229$, $p = 0.279$; Fig. S5). The temporal stem (TS) width asymmetry in controls (larger on the right) was lost in uWS patients (Fig. 2; ANOVA interaction term $F = 5.099$, $p = 0.033$). The planum temporale (PT) was larger on the right in controls and patients (within-subject effect for controls and patients combined $F = 4.327$, $p = 0.048$; Fig. S6).

Temporal lobe volume and brain volume with age. The total temporal lobe volume from manual volumetry (sum of left and right temporal lobe volumes) increased with age in patients and controls (for the combined sample of controls

and patients, Pearson's $r = 0.282$, $p = 0.005$ for total temporal lobe volume).

Temporal lobe differences between uWS patients and controls. The TS width was smaller bilaterally in uWS patients (Fig. 2; between-group main effect on ANOVA: F value = 23.84, $p < 0.0001$). The PT width was bilaterally smaller in uWS patients (between-group main effect on ANOVA F -value = 5.40, $p = 0.029$; Fig. S6). The two groups did not show a statistical difference for temporal lobe volume (between-group main effect on ANOVA: F value = 2.348, $p = 0.138$).

Treatment and MR data. The duration from initiating treatment to electroclinical remission (or time to effectiveness of treatment, TE) showed a relationship with the VBM total GM volume on post hoc regression (Pearson's $r = -0.630$, $p = 0.009$, Fig. S7). The potential impact of steroid treatment was assessed. Of the five patients who received high-dose oral prednisolone as initial treatment, four subsequently received vigabatrin (VGB) for recrudescence of spasms. The TE was the duration from the initial onset of spasms to the resolution of spasms and hypsarrhythmia after VGB. A hierarchical multiple regression model (predictor variables = treatment with steroids, TE; response variable = gray matter volume) did not find a significant effect of steroid treatment in the model as a predictor of GM ($\beta = 0.246$, $p = 0.165$). Further regression analysis excluding steroid-treated patients resulted in a loss of the TE-GM volume association ($r = -0.630$, $p = 0.009$ when the steroid-treated cases were included; versus Pearson's $r = -0.394$, $p = 0.106$ when the steroid-treated cases were excluded). The exclusion incurred a loss of statistical power, however.

Diffusion tensor imaging

DTI analysis using TBSS did not demonstrate a difference in brain fractional anisotropy and mean diffusivity between patients and controls.

Event-related potentials

The ERP response to repetition of a 1,000 Hz pure tone auditory stimulus in controls was a decrement of amplitude and latency, termed repetition attenuation (RA). The amplitude RA was significant over 100 repetitions in controls ($R = 0.783$, $p = 0.007$), but not in patients ($R = 0.236$, $p = 0.511$). The amplitude RA was right lateralized in both controls and patients, being greater over the right mid-temporal lobe (T4) than over the left (T3) (within-group ANOVA $F = 8.357$, $p = 0.006$). The mean N100 amplitude over the 100 stimuli did not differ between controls and patients ($F = 0.081$, $p = 0.777$), but there was a stimulus \times group interaction at the mid-temporal electrodes (T3 and T4) (repeated-measures ANOVA $F = 2.922$, $p = 0.002$; Figs. S8 and S9). The N100 latency

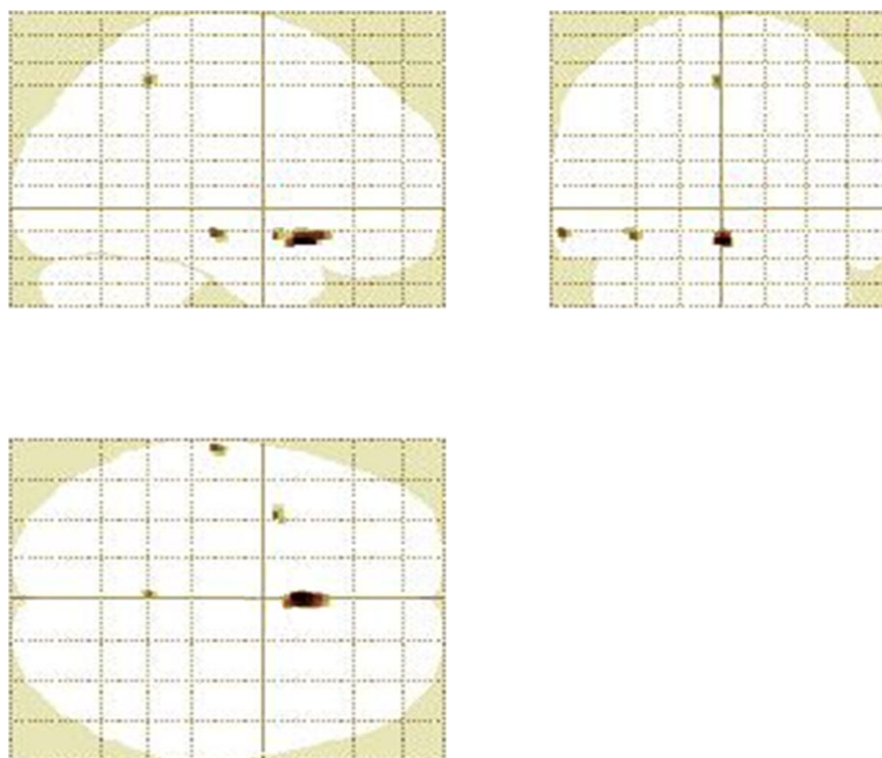


Figure 1.

Statistical parametric map output for voxel-based morphometry (VBM) on a glass brain showing increased gray matter volume in patients compared to controls at the middle temporal gyrus; the perirhinal cortex, and the medial temporal lobe (spatial threshold of 8 mm, with family-wise error $p < 0.005$).

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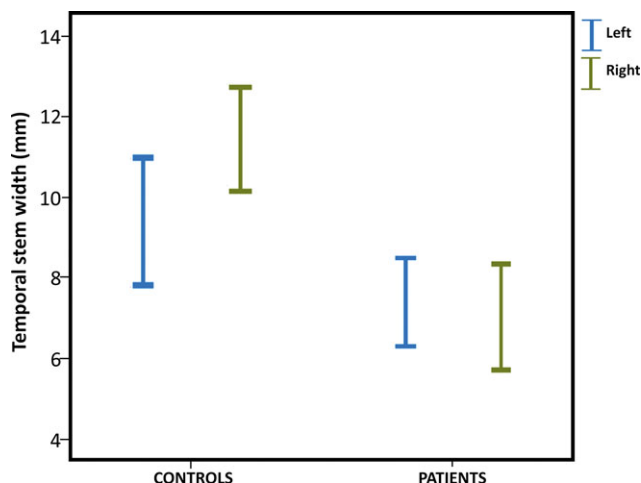


Figure 2.

The temporal stem width was reduced in uWS patients, particularly on the right. uWS patients showed a smaller ratio of right-to-left temporal stem width than controls.

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was prolonged in uWS patients (ANOVA $F = 5.988$, $p = 0.019$; see Table S3, Fig. S10).

The amplitude RA and the latency RA did not correlate with the size of the temporal lobe, PT, or TS in patients or controls ($p = \text{NS}$). The effect of treatment lag on the N100

latency over the left mid-temporal region (T3) was significant. The latency was shorter for short lag (under 1 month) than long lag (over 1 month) (latency mean [standard deviation, SD] 204 [19.9] vs. 224 [14.5]; $t = -2.495$, $p = 0.02$).

Bayley Scales of Infant Development II

BSID-II scores for patients differed significantly from those of controls ($p < 0.001$; Table 3), showing a median cognitive, language, and motor performance within the moderate impaired range (Fig. S11).

DISCUSSION

Brain structural development following infantile spasms

This study found two main changes in the temporal lobes of WS patients: the gray matter in patients' temporal lobes was increased, with a leftward emphasis; and TS WM volume was smaller bilaterally. The GM increase affected portions of the language-processing network, including the superior and middle temporal gyri, and the medial temporal lobe. The cause is undetermined, but childhood-onset idiopathic epilepsies also show increased temporal lobe GM.¹⁹ Thus, the finding in uWS may be epilepsy related.

There is no published information on the effect of infantile spasms on language dominance, but early onset epilepsy

Table 3. Bayley Scales of Infant Development, Second Edition (BSID-II) scores

	Controls median (range)	Patients median (range)	Mann-Whitney two-tailed significance (p-value)
Cognitive	100 (55–120)	55 (55–90)	<0.001
Language	91 (47–115)	55 (47–95)	<0.001
Motor	94 (46–115)	55 (46–94)	<0.001

Statistically significant values shown in bold.

is known to degrade left temporal lobe language function.²⁰ This is often accompanied by compensatory change in the language network.²¹ The left hemisphere's more protracted maturational course confers on it a longer period of vulnerability.²² The treatment data in this study would suggest more marked neuroplasticity of the left temporal lobe receptive language network following spasms. Manual volumetry was used to investigate the temporal lobe language cortex further. The size of the PT, an auditory association area shown to be important for the acquisition of language,²³ was assessed. The controls (infants in the second half of the first year of life) showed rightward size asymmetry of the PT. Previous work shows that the PT asymmetry is leftward shortly after birth,²⁴ so that it would mature to the rightward asymmetry observed here in the second half of infancy. Patients showed the same the rightward asymmetry of the PT as controls. A key event in the normal structural plasticity of the right temporal lobe has therefore occurred prior to the structural abnormalities of the temporal lobe described in this article. This tends to support the notion that the right temporal lobe is better developed than the left in the usual age-group affected by infantile spasms.

The study may be interpreted as evidence for preexisting difference in cortical maturation in uWS patients, which influences treatment responsiveness. Primary disorders of brain structural organization and maturation can affect brain MRI signal and clinical course. Subtle cortical dysplasias (CDs) produce VBM GM increase²⁵ and treatment-resistant spasms.²⁶ The uWS group lacked a focal electroclinical picture and had normal MRI results. The putative undiagnosed subtle CD does not, in the authors' opinion, adequately explain the study findings. An alternative inference is that early spasm remission "rescues" GM from the recognized deleterious effects of intense epileptiform activity in early life.²⁷ This manifests as (anti)correlation of TE with GM volume in uWS.

The psychometric profile of West syndrome

The psychometric profile of uWS patients published here is important, as standardized psychometric testing is not commonly reported in WS.¹⁸ The BSID-II has a twofold advantage. It is validated for ages 1–42 months,¹⁷ and shows more reliable test performance characteristics over the Griffith Mental Development Scale and the Vineland

Adaptive Behavior Scales in our study age group.²⁸ The limited cognitive impact achieved using current treatment is highlighted by patients' median BSID-II cognitive score being 45 units (3 SD) below that of controls. In a clinical sample, BSID-II cognitive score difference of 30 units (2 SD) in young children was noticeable clinically. This corresponded to a transition of cognitive performance (normal ability, disability, severe disability).²⁹

This study demonstrates that BSID-II can detect differences, including for language, between successfully treated uWS patients and normal children. Language acquisition is highly complex and poorly understood, and assessing receptive language in nonverbal infants is challenging.³⁰ Consequently, aERPs have proved useful in studying language in early childhood, measuring auditory processing ability which predicts early language development.³¹ The N100 ERP in uWS was prolonged, failing to shorten with stimulus repetition (Fig. S8). The observation of prolonged aERPs in treatment-controlled nonlesional epilepsies is not new.³² Shorter treatment lag minimized the N100 prolongation in uWS, supporting the idea that epilepsy can produce persistent effects on the brain's functional networks.

This work suggests that structural change in the temporal lobe is an epilepsy-related effect, which has consequences on language function following infantile spasms. A statistical correlation could not be demonstrated between structural changes in parts of the temporal lobe and clinical or ERP measures of language ability. This could, in part, reflect the network scale of functional effects in uWS. The statistical data in the study considered together suggest the following. The structural integrity of components of the temporal lobe language network may be regarded as necessary for its cognitive function, but with discrete areas not being sufficient for this. This situation would make the networking of the temporal lobe via its WM connection a key factor in long-term cognitive difficulties in uWS patients.

The connection architecture following infantile spasms

This study raises the possibility that epilepsy in infancy affects temporal lobe WM development. The expansion of WM occurs during childhood, and the quantity of temporal lobe WM predicts language abilities.³³ The general rule in mammals is conservation over evolution of the adult GM-to-WM ratio.³⁴ The teleologic role of expansion of WM appears to be to meet a "minimal wiring" requirement for a larger brain size.³⁴ This notion predicts that the reduced WM in patients is accompanied by a change in the connection pattern of the cortex. The structural basis of this putative alteration of WM connection architecture in uWS was probed using DTI at typical spatial resolution (2.5 mm isotropic). A difference of WM in patients relative to controls was not demonstrated. The concern exists that the complex evolution of DTI metrics in infancy³⁵ would limit the yield of DTI in infants. There is, however, no evidence that

DTI has reduced sensitivity in infants. Simulations indicate that DTI analysis in infants provides useful assessment of WM.³⁶ The negative DTI TBSS findings in this study could potentially signify an amelioratory effect of treatment. Further studies to evaluate this possibility are indicated.

LIMITATIONS

This cross-sectional study was performed during, but separately from, patients' routine clinical care. The absence of paired (pre- and posttreatment) data precluded a determination of whether treatment improved (or worsened) MRI, ERP, and psychometric measures. The instrumental measure of language (BSID-II) was limited by a floor effect, weakening correlation analyses to structural MRI and ERP data. Further instruments are required, and the third version (BSID-III) might be advantageous for future WS studies due to less of a floor effect for Language and Cognition scores.³⁷

The validity of VBM is contingent on two assumptions: accurate and complete segmentation of cortical gray matter from white matter T₁ signal intensity, and emission of identical signal intensity from the same tissue in patients as in controls. Segmentation is challenged by the well-described change in T₁-signal contrast over infancy. T₁ intensity is initially higher in GM than WM, but GM T₁ signal intensity decreases, whereas that of WM increases.³⁸ The period of isointensity between GM and WM T₁ signals varies by region, creating a potential for segmentation error that is nonmatched between the two groups if their brain regions mature differently. This study used a TPM from 2-year-old children for segmentation.¹⁶ Because of the higher T₁ intensity in infancy than at 2 years, GM in both groups of infants could be underestimated, being misclassified as WM. The GM difference between the groups may therefore be more extensive than found here. The use of the TPM from 2-year-olds and a customized infant brain template for VBM avoided the problems created by use of the standard adult version to study children.³⁹ The second assumption cannot be guaranteed to hold under all circumstances. Histologically, GM comprises dendrites (31%); axon collaterals (29%), and cell bodies (11%).⁴⁰ Thus, it is possible that abnormal MRI signal from axons within GM, rather than a definite volume increase of dendrites and cell bodies, accounts for the VBM findings in uWS.

The impact of these potential limitations on the performance of VBM in infancy is difficult to quantify. In practice, the high GM volume in the first year permits processes within GM to be captured by VBM, yielding biologically plausible results.⁴¹

Treatment is a potential confound in comparisons of patients and controls. The MR data for controls were acquired unmedicated, whereas chloral hydrate sedation was used for patients. The impact of sedation on MR signals is unknown, but the authors consider important effects to be

unlikely. The use of steroids by a minority of patients presents a confound, as these can reduce GM volume.⁴² Hierarchical regression did not find steroid treatment to be a statistically significant effect on the TE-GM volume relationship. VGB use by the majority of patients could, in theory, have produced the observed structural MRI changes on MRI rather than these being related to effects of epilepsy. The WM reduction in the temporal lobe was not greater in patients who had received VGB compared to those who had received steroids. Further studies with a larger comparison sample of steroid-treated uWS patients will clarify the role, if any, of VGB in impairing structural plasticity in the developing brain. There is published evidence that VGB can produce MR signal changes in the deep nuclei and brainstem in some patients with WS.⁴³ These MRI changes were not present in any of the patients recruited into this study. The VGB neurotoxicity to WM found in experimental animals has not been demonstrated unequivocally in humans either on MRI or in surgical neuropathologic specimens from adults and children.⁴⁴ A single human case has been reported with histopathologic WM changes following VGB.⁴⁵ The features of the case did not permit a causative relationship to be established. The infant had preexisting white matter damage, showing leukomalacia on MRI (due to preterm birth). On the anticonvulsant combination of VGB added on to topiramate, the patient experienced a febrile illness with encephalopathy and subsequently died of bronchopneumonia. Brain MRI and cerebrospinal fluid (CSF) studies were not performed during the acute illness, and infectious and inflammatory encephalitides were not excluded.⁴⁵ These could have caused the acute neurologic deterioration and postmortem histopathologic changes in WM.

CONCLUSION

This study provides new data on the structure of the temporal lobe following infantile spasms. The temporal lobe gray matter volume was increased in patients, and its white matter volume was reduced. The increased GM volume within the temporal lobe on VBM may reflect structural plasticity induced by epileptiform activity or its treatment. ERPs revealed a processing disorder for auditory rhythm in uWS. Treatment with vigabatrin did not normalize the structural or ERP findings, but more rapid control of infantile spasms may have minimized these. It remains to be determined through follow-up work whether the observed structural plasticity within the temporal predicts cognitive difficulties of patients.

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DISCLOSURE

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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ADDITIONAL CONTRIBUTORS

Professor Brian Neville (BN) conceived the study. Dr. Chris A. Clark (CAC) designed the MRI pulse sequences for the DTI study. Dr. Wukeyan "Kling" Chong (KC) provided training in the anatomy of the temporal lobe. Dr. Tanguu Fosi (TF) performed the manual volumetry of the temporal lobe. TF and Dr. Carlton Chu (CC) performed the semiautomatic volumetric analysis (VBM). Dr. Stewart Boyd (SB) designed and supervised the ERP experiments. TF performed the ERP experiments, measurements, and data analysis. Dr. Michelle De Haan (MD) performed psychometric testing of the uWS patients. Dr. Rod C. Scott (RC) and all the authors contributed intellectually to the content of this work. All authors approved the final version of this manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Data S1. Methods.

Table S1. The control characteristics.

Table S2. Magnetic resonance imaging pulse sequences.

Table S3. ERP data.

Figure S1. VBM segmentation output showing gray matter and white matter in a control.

Figure S2. Controls showed a significant difference between their whole-brain GM and WM volumes, whereas uWS patients did not show this difference.

Figure S3. Statistical parametric map output for conjunction VBM analysis displayed on a glass brain in neurologic convention.

Figure S4. The dimensions of the temporal lobe measured by manual volumetry.

Figure S5. The temporal lobe volumes in controls and uWS patients did not show a statistically significant difference.

Figure S6. The planum temporale width is normally larger on the right than on the left in infancy, as found in controls.

Figure S7. The correlation between gray matter volume and duration of hypsarrhythmia.

Figure S8. The group mean N100 amplitude over 100 repetition response of a 1,000 Hz tone in controls and patients measured at the mid-temporal lobe electrodes (T3, T4).

Figure S9. The repetition attenuation (Δ amplitude N100) at the mid-temporal lobe electrodes (T3, T4) in the control and uWS patient groups.

Figure S10. The N100 latency was prolonged in patients compared to controls at the mid-temporal lobe electrodes (T3, T4).

Figure S11. Bayley scores in patients and controls.

Figure S12. Correlation between voxel-based morphometry (VBM) and manual volumetry based gray matter measures.