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# Topographical Distribution of Epileptogenic Tubers in Patients With Tuberous Sclerosis Complex

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## Abstract

Tuberous sclerosis complex is a multisystem genetic syndrome often affecting the central nervous system. The purpose of the current study was to identify topographical patterns in the distribution specific to epileptogenic (n = 37) and nonepileptogenic (n = 544) tubers throughout the brain for a cohort of 23 tuberous sclerosis complex patients with a history of seizures. Tubers localized to the inferior parietal lobes, middle frontal lobes, middle temporal lobes, or central sulcus regions were associated with a high frequency of epileptogenic tubers. Epileptogenic tubers occurred statistically more frequently within the inferior parietal lobe and within the central sulcus region in children younger than 1 or between 1 and 3 years old, respectively. Results imply seizure activity in tuberous sclerosis complex patients can be associated with the location of cortical tubers.

## Keywords

tuberous sclerosis complex, tuberous sclerosis complex, population maps, analysis of differential involvement, seizures, epilepsy, topographic mapping

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Tuberous sclerosis complex is a multisystem genetic syndrome often affecting the central nervous system. Tuberous sclerosis complex is thought to occur as a result of mutation to 1 of 2 major genes: *TSC1*, which codes for the protein harmartin, and *TSC2*, which codes for tuberin.<sup>1,2</sup> As a result, tuberous sclerosis complex is believed to affect anywhere from 1 in 5000 to 1 in 10 000 individuals,<sup>3,4</sup> manifesting as a combination of seizures, mental retardation, and facial angiofibromas<sup>5</sup> along with other clinical features.<sup>6,7</sup> Tuberous sclerosis complex most often presents as seizures at the time of diagnosis,<sup>8,9</sup> with the majority of patients refractory to anticonvulsant drugs, making surgical intervention to control seizures a desirable treatment option.<sup>10-14</sup> Surgical intervention to control focal epilepsy in tuberous sclerosis complex patients can be difficult, however, since these patients often have multiple tubers, many of which are nonepileptogenic.<sup>15</sup> As such, advanced imaging techniques have been explored as promising ways for delineating epileptogenic from nonepileptogenic tubers for the purposes of surgical intervention.<sup>16</sup>

A number of studies have suggested the number and general location of cortical tubers can be associated with seizure activity and cognitive development in patients with tuberous sclerosis complex.<sup>17-23</sup> In particular, data have suggested an

increased number of tubers and tubers within the frontal, temporal, and posterior parietal lobes can result in increased seizure activity and delay in development.<sup>20,21</sup> This hypothesis

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appears relatively intuitive, considering that cortical tubers localized to specific areas of the brain can cause disruption in normal neurological function. However, recent studies have not found such a strong association between number of tubers, general location of these tubers (eg, temporal, frontal, parietal, or occipital lobes), epileptic activity, and cognitive development<sup>24-26</sup>. Since some tuberous sclerosis complex patients can have a single tuber with epileptogenic activity and other patients can have multiple tubers but no history of seizures, previous approaches aimed at merely quantifying the number of tubers per lobe might not be appropriate. In addition, previous studies have not identified the *specific* tuber or tubers associated with seizure foci, but instead have drawn an association between global distribution of tubers and the presence of seizure activity. Furthermore, the specific imaging phenotypes of cortical tubers described by Gallagher et al<sup>27</sup> as well as age of the patient can also play a significant role in epileptogenic tuber location, as these have both been shown to impact patient prognosis.

The purpose of the current study was to identify topographical patterns in the distribution specific to epileptogenic and nonepileptogenic tubers throughout the brain in stereotactic atlas space for a cohort of tuberous sclerosis complex patients with a history of seizures, and describe how these patterns vary by age groups and imaging tuber phenotypes.

## Methods

### Patients

A total of 23 patients diagnosed with tuberous sclerosis complex were enrolled in the current retrospective, Health Insurance Portability and Accountability Act-compliant, Institutional Review Board-approved research study (Table 1). Three patients were scanned at 2 time points, resulting in a total of 26 tuber scan sessions. A total of 581 tubers from these patients were identified, of which 37 tubers were determined to be epileptogenic, based on the multimodality presurgical evaluation (Table 2).

### Magnetic Resonance Imaging

Data were collected on either a 1.5 T (Signa HDx or Genesis, General Electric Medical Systems, Waukesha, WI; Avanto or Sonata, Siemens Healthcare, Erlangen, Germany) or 3 T MR system (Trio, Siemens Healthcare, Erlangen, Germany) using pulse sequences supplied by the manufacturer. Standard anatomical magnetic resonance imaging (MRI) sequences included pre- and postgadolinium (Gadolinium Diethylenetriaminepentaacetic acid (Gd-DTPA) at a dose of 0.1 mmol/kg body weight; Magnevist, Bayer Schering Pharma, Leverkusen, Germany) axial T1-weighted (echo time/repetition time = 8-15 ms / 400-700 ms; slice thickness = 3-5 mm with 0-1 mm interslice gap; number of excitations/averages = 2; matrix size = 256-512 × 192-260; and field of view = 14.6-20 cm<sup>2</sup>), axial T2-weighted fast spin-echo (echo time/repetition time = 81-144 ms/2200-6000 ms; slice thickness = 3-5 mm with 0-1 mm interslice gap; number of excitations/averages = 2; matrix size = 256-512 × 192-256; and field of view = 15-20 cm<sup>2</sup>), and axial fluid-attenuated inversion recovery images (inversion time = 2200-2500 ms; echo time/repetition time = 83-157 ms/7000-9000 ms; slice thickness = 4-5 mm with 0-1 mm

**Table 1.** Patient Characteristics.

Patient (surgery)	Age	Sex	Surgery
1	11m	M	Y
2	12y2m	M	Y
3	9m	F	Y
3(2)	1y9m	F	Y
4	10m	M	Y
5	2y2m	F	Y
6	5y	F	Y
7	5m	M	Y
8	4y10m	F	Y
9	2y2m	M	Y
10	8y10m	M	Y
11	1y4m	M	Y
12	1y8m	F	Y
13	9y6m	F	Y
14	3y6m	F	Y
14(2)	4y10m	F	Y
15	4y10m	F	Y
16	1y6m	M	Y
17	5y9m	F	Y
18	10y5m	F	Y
18(2)	11y6m	F	Y
19	5y1m	M	Y
20	7y11m	F	Y
21	19y6m	F	Y
22	3y6m	F	Y
23	2y	M	Y

interslice gap; number of excitations/averages = 1; matrix size = 256-512 × 154-280; field of view = 15-20 cm<sup>2</sup>).

### Image Registration to Montreal Neurological Institute Atlas Space

All images for each patient were registered to a 1.0-mm isotropic T1-weighted brain atlas (Montreal Neurological Institute 152) using a 12-degree of freedom affine transformation and mutual information cost function and through the FMRIB Software Library from FSL (<http://www.fmrib.ox.ac.uk/fsl/>). This was followed by visual inspection to ensure adequate alignment, including maintaining proper positioning of the ventricular and cortical surface relative to the atlas as well correspondence between the location of most cortical gyri and sulci. The contour of the lesion was verified using superposition of fluid-attenuated inversion recovery and T1-weighted images.

### Regions of Interest

Regions of interest were created for all 581 cortical tubers from 23 tuberous sclerosis complex patients after identification on T2 or fluid-attenuated inversion recovery anatomical MRI. Tubers were manually contoured slice by slice and uniquely labeled for identification and subsequent analyses.

### Identification of Epileptogenic Tubers

Suspected epileptogenic tubers were first identified using advanced neuroimaging and monitoring methods that included combinations of ictal and interictal video-electroencephalography, interictal

**Table 2.** Tuber Characteristics.

		Number of scan sessions	Number of patients	Number of epileptogenic tubers	Number of nonepileptogenic tubers	Total number of tubers
Age	0-6 months	1	1	2	14	16
	7-12 months	3	3	5	69	74
	1-3 years	9	9	11	172	183
	4+ years	13 <sup>a</sup>	12 <sup>a</sup>	19	289	308
	Total	26 <sup>b</sup>	23 <sup>b</sup>	37	544	581
Radiographic phenotype	Type A	26 <sup>b</sup>	23 <sup>b</sup>	5	247	252
	Type B	26 <sup>b</sup>	23 <sup>b</sup>	23	267	290
	Type C	12 <sup>c</sup>	11 <sup>c</sup>	9	30	39
	Total	26 <sup>b</sup>	23 <sup>b</sup>	37	544	581

<sup>a</sup>12 patients with 13 scans were acquired. One patient (number 18) had an MRI scan at 2 time points after age 4 (the first and second surgeries).

<sup>b</sup>23 patients with 26 scans were acquired. Three patients (numbers 3, 14 and 18) had MRI scans at 2 time points (the first and second surgeries).

<sup>c</sup>11 patients with 12 scans were acquired. One patient (number 3) had an MRI scan at 2 time points (the first and second surgeries).

magnetoencephalography, and/or interictal fluorodeoxyglucose positron emission tomography (PET).<sup>28,29</sup> The specific tubers responsible for seizure activity were then verified through surgical resection and a reduction in post surgical seizure activity.

### Imaging Tuberos Sclerosis Complex Phenotypes

Each tuber was categorized according to their distinct radiographic phenotype as outlined by Gallagher et al based on how they manifest on T1-weighted, T2-weighted, and T2-weighted fluid-attenuated inversion recovery images (Figure 1). Type A tubers are more mild tubers, appearing isointense on T1-weighted images and subtly hyperintense on T2-weighted and fluid-attenuated inversion recovery. Type B tubers are characterized by hypointensity on T1-weighted images and homogeneous hyperintensity on T2/fluid-attenuated inversion recovery. Type C tubers have characteristics related to a more cystic tuber, namely hypointensity on T1-weighted images, hyperintensity on T2-weighted images, and heterogeneous enhancement patterns on fluid-attenuated inversion recovery (hypointense central region surrounded by a hyperintense rim). Type C tubers have more severe clinical consequences,<sup>27</sup> including higher frequency of subependymal giant cell tumors, a higher likelihood for autism spectrum disorder, and a higher frequency of epileptic seizures.<sup>28</sup> The distribution of tubers across these different phenotypes is shown in Table 2.

### Analysis of Differential Involvement

Analysis of differential involvement consisted of implementing a 2-tailed Fisher's exact test to evaluate a  $2 \times 2$  contingency table comparing epileptogenic versus nonepileptogenic tuber versus nontuber for each image voxel. This type of analysis has previously been implemented to identify regions specific to various biological phenotypes in brain tumors.<sup>30,31</sup> According to Fisher's exact test, the probability of obtaining the observed "pattern" in the  $2 \times 2$  contingency table for each voxel is given by the hypergeometric distribution:

$$P = \frac{(a+b)!(c+d)!(a+c)!(b+d)!}{a!b!c!d!n!}$$

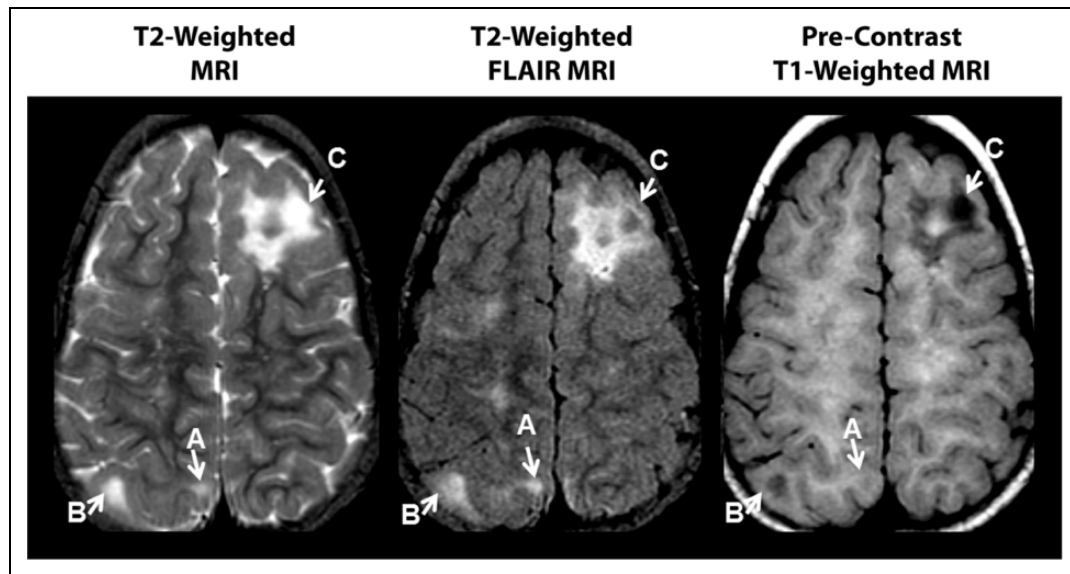
where  $a$  is the number of epileptogenic tubers occurring at the current voxel location;  $b$  is the number of epileptogenic tubers *not* occurring at the current image location;  $c$  is the number of nonepileptogenic

tubers occurring at the current voxel location; and  $d$  is the number of nonepileptogenic tubers *not* occurring at the current image voxel. To calculate the significance of the observed pattern in the contingency table as extreme or more extreme, the  $P$  value for each voxel needs to be recalculated for all cases where the marginal totals are the same as the observed tables, and only cases where the arrangement is as extreme as the observed pattern. The final  $P$  value represents the probability of observing the given pattern in the contingency table, or simply the probability that the pattern of tuber occurrence happened by chance. A  $P$  value for a specific voxel less than .05 was considered significant.

After quantification of  $P$  value and isolation of statistically significant voxels, a cluster-based multiple comparison correction technique was used as outlined by Bullmore et al.<sup>32</sup> Briefly, tubers were first assigned randomly to each category (epileptogenic vs nonepileptogenic), statistical testing using Fisher's exact test was repeated, and the size of statistically significant clusters was documented. This process was repeated 100 times to determine how likely a specific cluster size would occur due to chance. Results from the permutation analysis suggested less than a 5% chance of obtaining cluster sizes larger than 1 cc when considering all tubers, considering tubers within age groups, and when considering tubers within radiographic phenotypes.

### Results

Examination of the spatial distribution of all tubers throughout the brain in stereotactic space (Figures 2A, 2B) showed a relatively even distribution throughout the cortex and superficial white matter. Results indicated tubers localized to specific areas were more likely to contain epileptogenic activity (Figures 2C-2F). Statistical analysis suggested 4 specific clusters were significantly more likely to contain epileptogenic tubers compared with nonepileptogenic tubers. Cluster A (Figures 2C, 2G) was spatially localized to an 8.5 cc cluster and had the highest localized level of statistical significance. This cluster was localized to the supramarginal gyrus and the inferior parietal lobe (Brodmann area 40), or areas associated with spatial orientation, semantic representation, and attention



**Figure 1.** Radiographic tuberous sclerosis complex Phenotypes from Gallagher et al observed in a single patient. Type A: high intensity in T2, fluid-attenuated inversion recovery (FLAIR) and Iso intensity in T1-weighted image. Type B: high intensity in T2, FLAIR and low intensity in T1-weighted image. Type C: high intensity in T2, heterogeneous intensity in FLAIR, and low intensity in T1-weighted image.

networks. Cluster B (Figures 2D, 2G) measured 9.7 cc and was diffusely spread over the caudal portion of both the superior and inferior temporal sulci along with the middle temporal gyrus (approximately in Brodmann areas 37 and 33). Cluster C (Figures 2E, 2G) had a cluster size of 2.7 cc and was localized to the central sulcus, extending into both the pre- and postcentral gyri (Brodmann areas 3 and 4). Last, Cluster D (Figures 2F, 2G), measuring 1.6 cc in volume, appeared concentrated in the rostral aspects of the middle frontal gyrus (Brodmann area 46).

### Epileptogenic Tuber Localization by Age

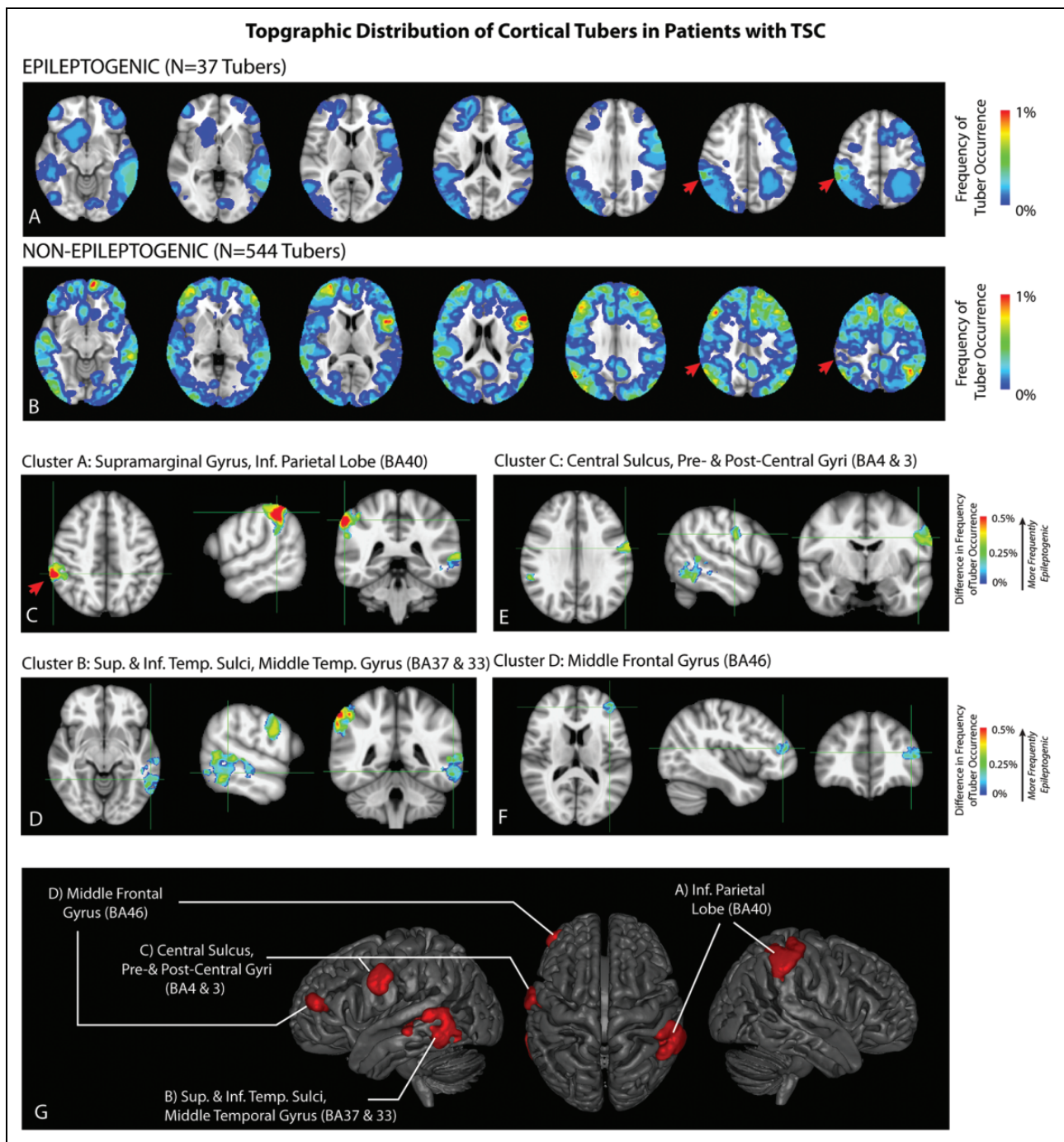
Patients were stratified by age to identify age-related patterns in epileptogenic tuber location (Figure 3). Results suggest children with tuberous sclerosis complex less than 3 years of age had more epileptogenic tubers localized to 2 specific regions, the supramarginal gyrus and inferior parietal lobule (Figure 3A; volume = 6.1 cc), and diffuse regions across the central sulcus, extending into the pre- and postcentral gyri (volume = 5.6 cc). No region-specific statistical trends were found with respect to epileptogenic tuber location in patients with tuberous sclerosis complex older than 4 years of age. Interestingly, further stratification of patients younger than 3 years old suggested the cortical region associated with the supramarginal gyrus and inferior parietal lobe were statistically associated with increased epileptogenic activity in patients younger than 1 year old (Figures 3B, 3D; volume = 4.2 cc), whereas the diffuse regions near the central sulcus were associated with increased epileptogenic activity in patients between 1 and 3 years old (Figures 4C, 4D; volume = 6.4 cc). Additional patient substratifications by age did not reveal any statistical patterns (eg, < 6 mo.; 7-12 mo; etc).

### Epileptogenic Tuber Localization by Radiographic Phenotype

Each tuber was characterized according to radiographic phenotype as outlined by Gallagher et al.<sup>27</sup> In general, epileptogenic type A tubers occurred more frequently in the medial frontal cortex, bilaterally (Figures 4Aa-b and 4D; volume = 4.2-4.4 cc), as well as bilaterally within the middle temporal sulcus (Figures 4Ac-d and 4D; volume = 1.5 -1.8 cc). Type B and C tubers both occurred most frequently in the inferior parietal lobe (Brodmann area 40) and along the supramarginal gyrus (Figures 4B-C and 4D; volume = 1.5 cc and 1.0 cc, respectively). A closer examination of these 2 regions showed slight differences in the topographic localization of type B and type C tubers (Figure 4D), with localization type B occurring slightly inferior to type C along the supramarginal gyrus.

### Discussion

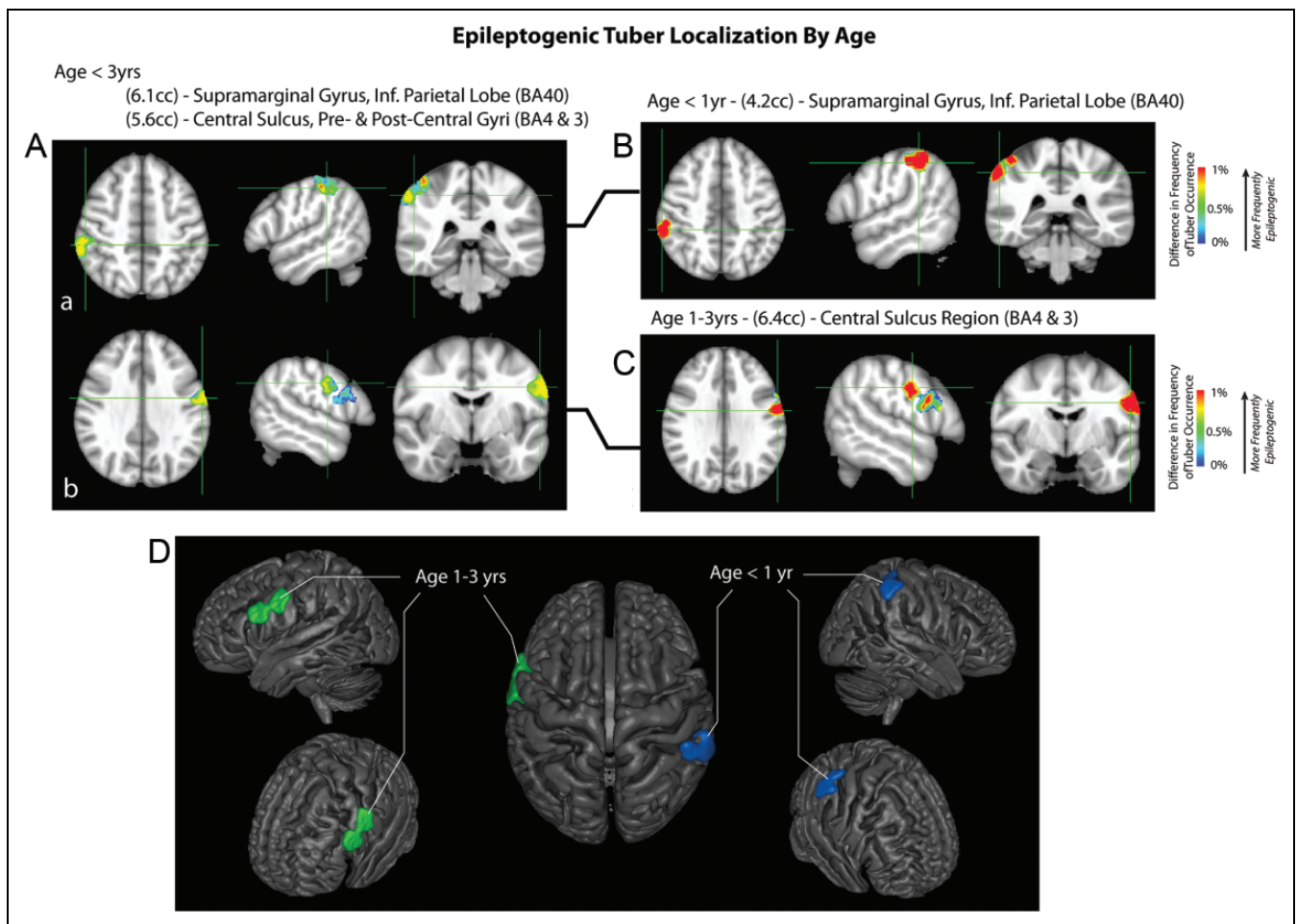
Most studies have described cortical tuber localization only in general terms (eg, particular lobes involved). Thus, to provide more stereospecificity of tuber localization and topographic distribution throughout the brain the authors have constructed "population maps" for various age groups and radiographic phenotypes for both epileptogenic and nonepileptogenic tubers. A similar approach involving mapping tuber location into a standard atlas space was proposed by Ridler et al<sup>33</sup> in high-functioning adults with tuberous sclerosis complex. Consistent with this study, the current authors observed a high density of cortical tubers localized to the right inferior parietal lobe. Results in the current study, however, suggest this area can also be preferentially associated with tubers having a high probability of epileptogenic activity.



**Figure 2.** Topographic distribution of cortical tubers in patients with tuberous sclerosis complex. Population maps showing topographic distribution of (A) epileptogenic and (B) nonepileptogenic tubers throughout the brain in standard stereotactic space. (C-F) Regions associated with a significantly higher frequency of epileptogenic tuber occurrence in tuberous sclerosis complex using analysis of differential involvement applied to all tubers. (C) Cluster A showing a large region (8.5 cc) localized to the supramarginal gyrus and the inferior parietal lobe. (D) Cluster B (9.7 cc) localized to the middle temporal gyrus. (E) Cluster C (2.7 cc) localized to the central sulcus, extending rostrally into the precentral gyrus and caudally into the postcentral gyrus. (F) Cluster D (1.6 cc) concentrated in the middle frontal lobe. (G) Volume rendered representation of regions shown to be associated preferentially with epileptic tuber locations. Note: Images are shown in radiographic orientation and 3D volumes are in physical space. Arrows highlight the inferior parietal lobe region most associated with epileptogenic activity.

The current study identified 4 regions of the brain that are significantly more likely to contain epileptogenic tubers: (1) the inferior parietal lobe (Brodmann area 40); (2) the posterior

portion of the middle temporal gyrus extending from the superior to the temporal sulci (Brodmann areas 33 and 37); (3) central sulcus extending into both the pre- and postcentral gyri



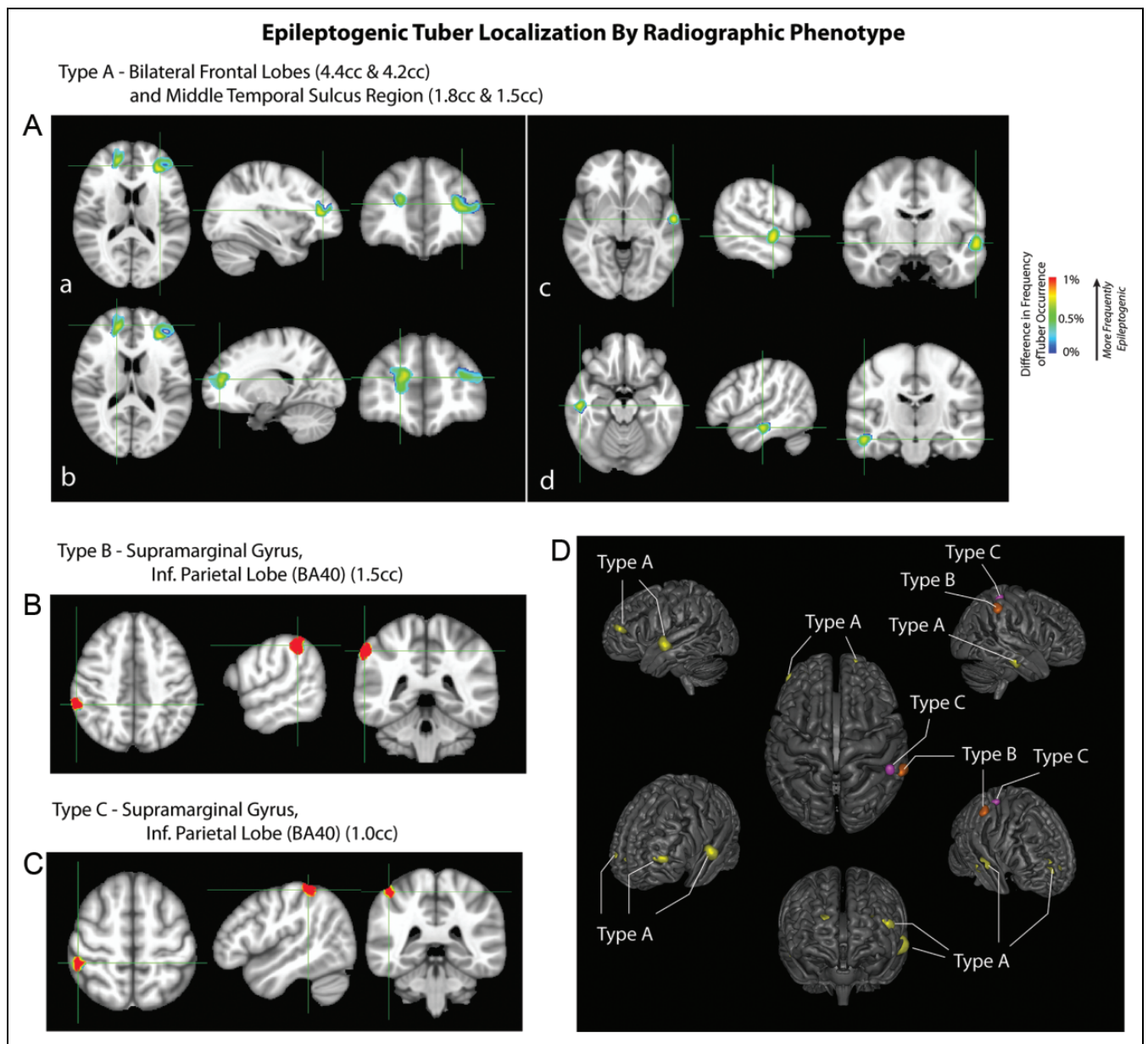
**Figure 3.** Topographic distribution of epileptogenic cortical tubers for young children (<3 years old) with tuberous sclerosis complex. (A) Statistical results for patients less than 3 years old illustrate a higher likelihood of epileptogenic tubers in (a) the inferior parietal lobe (6.1 cc) and (b) the central sulcus (5.6 cc). (B) Patients younger than 1 year old have a higher likelihood of epileptogenic tubers in the inferior parietal lobe, whereas (C) patients between 1 and 3 years old have a higher likelihood of epileptogenic tubers in the central sulcus. (D) Volume rendered representation of regions associated with statistically higher incidence of epileptogenic versus nonepileptogenic tubers for patients younger than 1 year old and patients between 1 and 3 years old.

(Brodmann areas 3 and 4); and (4) the middle frontal lobes (Brodmann area 46). When examining only young patients, tubers near the inferior parietal lobe were more frequently epileptogenic in children younger than 1 year of age whereas tubers within the central sulcus were more frequently epileptogenic in children between 1 and 3 years old. Further stratification of tubers by radiographic phenotype suggests type A tubers occur more frequently in the middle frontal and middle temporal lobes, whereas epileptogenic tubers with types B and C occur most frequently in the inferior parietal lobe. These results imply that tubers localized to these regions can result in a higher than normal likelihood of seizure activity, likely due to disruption of brain tissue within these important cortical regions. Results also suggest radiologists and clinicians should first suspect tubers within the inferior parietal, middle frontal, and middle temporal lobes as being most likely associated with seizure activity.

The current study is consistent with previous studies showing a significantly high density of tubers in the inferior parietal

lobe.<sup>21,33</sup> The presence of tubers in these locations has also been associated with a lower IQ score in tuberous sclerosis complex patients.<sup>21</sup> Within the left hemisphere, these areas of the brain are often considered part of the posterior language area. Interestingly, a series of studies by Gallagher et al<sup>34,35</sup> have shown diffuse changes in language representation and changes in language laterality in patients with tuberous sclerosis complex that appears to be dependent on the history of epilepsy and the presence of tubers in language areas. In particular, these investigators demonstrated that patients with tuberous sclerosis complex having a history of epilepsy or presence of tubers within language areas showed bilateral language patterns.<sup>34</sup>

In addition to regions associated with language networks, the authors also observed areas within the middle temporal gyrus associated with a higher probability of epileptogenic tubers. Consistent with these results, Chou et al<sup>20</sup> found that the tuber load and presence of a large tuber burden in the temporal



**Figure 4.** Topographic distribution of epileptogenic cortical tubers for various imaging phenotypes. Population maps associated with epileptogenic tubers for various imaging phenotypes including: (A) Type A—mild tubers that appear isointense on T1-weighted images and subtly hyperintense on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images. Two bilateral regions were associated with a higher incidence of epileptogenic tubers including the middle frontal lobes (4.2 cc and 4.4 cc) and middle temporal sulci (1.5 cc and 1.8 cc). (B) Type B—tubers characterized by hypointensity on T1-weighted images and homogeneous hyperintensity on T2/FLAIR. Regions within the inferior parietal lobe (1.5 cc) were associated with a higher incidence of epileptogenic type B tubers. (C) Type C—tubers having characteristics related to a more cystic tuber, namely hypointensity on T1-weighted images, hyperintensity on T2-weighted images, and heterogeneous enhancement patterns on FLAIR. Regions within the inferior parietal lobe (1.0 cc) were also associated with a higher incidence of epileptogenic type C tubers. (D) Volume rendered regions within the inferior middle temporal lobes, middle frontal lobes, and right parietal lobe associated with incidence of epileptogenic tubers for different imaging phenotypes.

lobes were associated with worse neurological prognosis. Many of these patients showed larger area of hypometabolism in fluorodeoxyglucose PET-MRI coregistration.<sup>28</sup> Furthermore, this area of the brain is commonly associated with epileptogenic behavior in a variety of seizure disorders. In addition, the presence of tubers within the temporal lobe has

been implicated in other comorbid neurological conditions including autism spectrum disorder,<sup>36</sup> however, this relationship remains controversial as other studies have not found such an association.<sup>19,37-39</sup> Since there is a high co-occurrence of autism spectral disorder and tuberous sclerosis complex<sup>40-42</sup> and evidence suggests early onset of electrophysiological



instability within the temporal lobes can result in impaired development of cognitive areas associated with processing of social information, results can support the hypothesis of an association between epileptogenic tubers in the temporal lobes in tuberous sclerosis complex and the presence of autism.

Interestingly, many of the regions harboring tubers that were found to be associated with increased epileptogenic activity appear to be consistent with regions associated with the “default mode network,” a network of interconnected brain regions<sup>43,44</sup> that are activated in synchrony during internal tasks such as retrieving memories. In particular, altered connectivity between regions of the medial temporal lobes, medial prefrontal cortex, and medial parietal cortex have been demonstrated in epilepsy patients.<sup>45,46</sup> These areas appear consistent with regions shown to be functionally involved in generalized and electroconvulsive therapy-associated seizure activity as measured using single photon emission computed tomography imaging.<sup>47</sup> Changes in the default mode network are also noted in autism and other social spectral disorders,<sup>43</sup> which occur at a high coincidence in patients with tuberous sclerosis complex.<sup>40-42</sup> In addition, the default mode network is known to emerge and evolve during normal development,<sup>48</sup> suggesting tuber development in these regions during childhood development can result in long-term disruption of the network and can likely explain why the authors observed changing topographic localization of epileptogenic tubers during the first years of life.

## Study Limitations

There were a few important limitations that need to be addressed. First, tuberous sclerosis complex results in large changes in brain morphology, including significant cerebral volume loss.<sup>49</sup> In addition, most of the patients included in the current study were adolescents. Thus, the standard Montreal Neurological Institute adult atlas might not accurately represent true anatomical brain regions affected by epileptogenic tubers. Another potential limitation to the current study was the variable number of epileptogenic and nonepileptogenic tubers for each tuberous sclerosis complex patient. In the current study the authors treated each tuber independently; therefore, patients with a higher number of tubers had more influence on the resultant population maps. More sophisticated statistical models are necessary to disassociate these effects. In addition, the authors chose only to include patients who underwent surgical resection and obtained seizure control to confirm the site of epileptogenic activity. This can have resulted in a highly selective cohort of patients included in the current study, which could have limited applicability to a larger population of tuberous sclerosis complex patients where seizure activity could not be localized or adequately defined. Last, the locations of a few temporal lobe epileptogenic tubers were estimated from the site of the postoperative resection cavities. Therefore, localization of epileptogenic foci for these patients was less precise and can have influenced the final results.

## Conclusions

In summary, the current study examined the topographic distribution of epileptogenic and nonepileptogenic tubers in patients with tuberous sclerosis complex. Statistical analyses noted 4 areas of the brain associated with increased likelihood of seizure activity, including the medial frontal, medial temporal, somatosensory, and inferior parietal regions. Topographic distribution of epileptogenic tubers varied by both age and radiographic phenotype. Results suggest radiologists and clinicians should give particular attention to tubers localized to these regions.

## Author Contributions

BEM: study design, image analysis, manuscript writing, reviewing, editing; YK: study design, image analysis, manuscript reviewing, manuscript editing; AY: study design, image analysis, manuscript reviewing, manuscript editing; EK: image analysis, manuscript reviewing, manuscript editing; KL: image analysis, manuscript reviewing, manuscript editing; DCW: image analysis, manuscript reviewing, manuscript editing; RJH: image analysis, manuscript reviewing, manuscript editing; DRE: study design, manuscript reviewing, manuscript editing; JYW: study design, manuscript reviewing, manuscript editing; GWM: study design, manuscript reviewing, manuscript editing; NS: study design, manuscript reviewing, manuscript editing.

## Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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## Ethical Approval

The current retrospective study was approved by the Institutional Review Board at the University of California, Los Angeles.

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