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The role of the corpus callosum in seizure spread: MRI lesion mapping in oligodendrogliomas

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Secondary generalization

Summary
Background: Some patients with oligodendrogliomas have generalized tonic—clonic seizures (GTCS) while others have only partial seizures (PS). We investigated the relationship between tumour localization and seizure generalization using quantitative lesion mapping on magnetic resonance images.
Methods: Twenty one patients with histologically proven oligodendrogliomas and GTCS ($n = 11$) or PS ($n = 10$) were studied. Data were acquired on a 3 Tesla MRI System. We performed lesion mapping techniques to compare the spatial distribution of oligodendrogliomas between patient groups, and quantitatively determined the extent to which lesions intersected each probabilistic regions-of-interest, including the cerebral lobes, thalamus, striatum, and genu of the corpus callosum.
Results: In patients experiencing GTCS, the greatest lesion load was observed in mesial frontal regions, including cortex connected to the genu. In contrast, the greatest lesion load in patients experiencing PS was observed more caudo-laterally in orbitofrontal and temporal lobes, but typically sparing cortex connected to the genu. The number of lesion intersections with genu region of interest was significantly greater in patients experiencing GTCS relative to patients with PS ($p = 0.03$). There were no significant differences between patient groups with

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respect to lesion intersection with the individual cerebral lobes, thalamus and striatum, or with respect to overall oligodendroglioma size.
Conclusion: Our data suggest that the genu of the corpus callosum may be a major pathway for seizure generalization in patients with oligodendrogliomas.
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Introduction

Epileptiform activity and clinically manifest seizures occur when a population of cells in the grey matter begins to fire excessively (Dodson, 2004). It is generally accepted that such pathological synchronized activity results from an imbalance of excitation and inhibition in cortical circuits at multiple levels. Seizure semiology and severity is determined by the spread of this synchronized activity to other parts of the brain. Seizure spread is very difficult to study because large parts of the brain are inaccessible for surface EEG. The study of seizure spread has been largely limited to the small minority of patients who have been investigated with invasive EEG as part of the pre-surgical work up for epilepsy surgery.

Oligodendrogliomas are intrinsic brain tumours that frequently present with epileptic seizures. About 70% of patients present with seizures (Ketz, 1974). Seizures can be the only manifestation of low grade gliomas including oligodendrogliomas (Morris et al., 1993). It is generally accepted that white matter, infratentorial and basal tumours are less epileptogenic then those in the cortex of the cerebral hemispheres. However, the types of seizures associated with brain supratentorial tumours have often been analyzed and widely divergent results have been obtained (Ketz, 1974). Some patients with oligodendrogliomas have only partial seizures, which may be fleeting sensations, resulting in a delay of the diagnosis. Other patients experience solely or predominantly secondary generalized seizures, often with an absence of, or very brief, aura. In the present study, we studied the relationship between seizure semiology and tumour location in a cohort of patients with oligodendrogliomas. In particular, using lesion-mapping techniques applied to MRI scans, we specifically explored the association between seizure type (generalized tonic clonic seizures (GTCS) or partial seizures (PS)) with tumour location.

Methods

Participants

The study was performed as part of an audit on oligodendrogliomas and was approved by the appropriate hospital review panel. We obtained a list of 151 patients with histological proven oligodendrogliomas from a neuropathological database. In 46 patients an MRI volume scan was available and we randomly selected 22 patients, one of whom had to be excluded because of artefacts on volume scans leaving eleven patients with GTCS and ten with PS. The patients had attended the Walton Centre over a timespan of 10 years. The average duration to surgery was for *gtcs 30 month (Standard deviation (SD) 40.5 month) and for PS 25.5 month (SD 39.4 month)*. The clinical data are shown in Table 1.

MRI analysis

MRI data were acquired on a 3 Tesla MRI System (Philips Achieva). Quantitative image analysis studies were performed on 3D T1-weighted images acquired axially (TR = 9.76, TE = 4.59, Flip Angle = 8, voxel size = 1 mm × 1 mm × 1 mm, image dimensions = 182 × 218 × 182). We performed a lesion-mapping technique to determine the topological distribution of oligodendrogliomas in standard space based on previously published methods (Rorden et al., 2007), with a goal of determining whether lesion load in a particular brain region was related to GTCS. Initially, all images were realigned into the same anterior commissure—posterior commissure orientation using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Realigned images were imported into MRIcron (www.mccauslandcenter.sc.edu/mricro/mricron) for manual delineation of lesions in native (subject-specific) space by KM, who was blinded to the clinical data. Oligodendrogliomas were delineated primarily in the acquired axial plane, with simultaneous reference to coronal and sagittal sections. Segmented lesions were saved as a separate file and binarised. We used FSL (The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library) tools (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki) for the spatial transformation of images and lesion segmentations to standard space, as previously done for lesion mapping. In particular, both affine (FLIRT; FSL Linear Image Registration Tool) and non-linear (FNIRT; FSL Nonlinear Image Registration Tool) transformations were used to register each image to the Montreal Neurological Institute (MNI) 152 coordinate system, which is a T1-weighted atlas constructed from 152 images in standard space (http://www.bic.mni.mcgill.ca/ServicesAtlases/ICBM152NLin6). The non-linear warps used to register images to the standard template were applied to the corresponding segmented binarised lesions, which transformed lesions into standard non-linear (MNI) space. Fig. 1 shows examples of lesion delineation and spatial normalization in two exemplar cases. FSL utility tools (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Fslutils) were used to determine the voxel-wise topology of lesions common to patients with GTCS and PS separately by concatenating all spatially normalised lesions into an individual image file per group (using 'fslmerge') and determining the number of times a voxel was intersected by a lesion (using 'fslmaths'). The result was a single image file that was colour-coded according to the number of times each voxel was lesioned for each group, and which was superimposed onto the MNI template MR image for neuroanatomical reference.

Lesion mapping provided an opportunity to visualise the differences in lesion load between the two patient groups. In order to test our hypotheses quantitatively, we determined whether each spatially normalized lesion intersected, and

Table 1 Clinical data.

Pat. No.	Gender	Age	Seizure type	Headache	Deficit
1	M	33	GTCS from sleep	n	n
2	F	41	GTCS	n	n
3	M	37	GTCS	y	n
4	M	35	GTCS from sleep	n	n
5	M	36	cps followed by GTCS same, also sensation r	y (coughing)	n
6	M	39	GTCS ×3 in 45 min	y	n
7	M	37	GTCS ×2 from sleep	n	n
8	M	32	GTCS ×4 within 3 months, 4 sps l side of face	n	n
9	F	38	GTCS	n	n
10	F	43	GTCS	y	n
11	M	49	GTCS	n	n
12	M	55	Amnesia whilst driving, 2 months ago RTA	n	n
13	M	67	Cannot find the right words, head jerks to r	N	y**
14	M	47	Sensation down l side of body	n	n
15	M	46	Pins and needles r leg 10s 5 to 6 a day	n	n
16	M	39	Numb mouth & tongue, cannot speak	y	n
17	M	37	Visual disturbance*,pins & needles r hand	n	n
18	F	39	''Neck spasms'' with repetitive head turning r	n	n
19	F	64	Writhing movements & twitching l arm & leg	n	y***
20	F	47	Flashing light r	n	n
21	F	43	Cannot speak	y	n

r = right, l = left, GTCS = generalized tonic clonic seizure
* Moving objects in the periphery.
** r upgoing plantar.
*** l pronator drift.

the proportion (volume) of each lesion intersecting, seven regions of interest (ROIs): (i) frontal lobes, (ii) temporal lobes, (iii) parietal lobes (iv) occipital lobes, (v) thalami, (vi) striatum, and (vii) fibres connected the genu of the corpus callosum. Lobar, thalamic and striatal ROIs were obtained from the MNI probabilistic brain atlas in standard space (Mazziotta et al., 2001; Fig. 2). The striatum was constructed by merging the putamen and caudate atlas masks. The genu ROI was also obtained from FSL software, and was generated from diffusion tensor imaging tractography maps in standard (MNI) space (Hua et al., 2008). We performed statistical analyses on categorical and continuous data. For categorical data, we used a Fisher's exact test to determine whether there was a difference between outcome groups with respect to whether or not lesions intersected a probabilistic ROI. Chi Square tests were used to investigate whether outcome groups differed in tumour size. For continuous data, the number of lesioned voxels intersecting each ROI was calculated using 'fslmaths' for each patient, from which a volume and percentage of each lesion intersecting each ROI was derived. A one-way ANOVA was used to compare the volume/percentage of lesion intersecting each ROI between patient groups. PSPS

Results

Clinical data

All 21 oligodendroglioma patients had epileptic seizures at presentation. Seizures were very stable and stereotypical. Patients who presented with partial seizures continued to have partial seizures, patients who presented with GTCS continued to have generalized seizures apart from patients five and eight (Table 1) who had a combination of focal and secondary generalized seizures. Six of 21 (35%) had also new onset headaches, and two of 21 (10%) had focal neurological deficits. GTCS and PS groups were similar in terms of age (Table 1). There was a small preponderance of men in the GTCS group. The 1p19q deletion was present in four patients with GTCS, absent in one and not available in six. In PS the 1p19q deletion was present in five, absent in two and not available in three.

MRI data

In our study the oligodendrogliomas were more commonly on the left side (14 left, seven right). Oligodendrogliomas were occasionally diffuse and could spread into basal ganglia and thalamus. Frontal and temporal involvement were most common. In patients with GTCS, the highest lesion load was observed in mesial frontal regions bilaterally, involving cortex connected to the genu of the corpus callosum (Fig. 3). Left-sided parietal lesions were also observed. In contrast, PSthe largest lesion load was observed more caudo-laterally in patients with PS, involving orbitofrontal, temporal and parietal regions (Fig. 4). It was visually evident that mesial frontal regions were substantially less affected in patients with PS relative to those with GTCS.

Eight of 11 (73%) patients with GTCS and two of ten (20%) patients with PS had lesions intersecting fibres from the

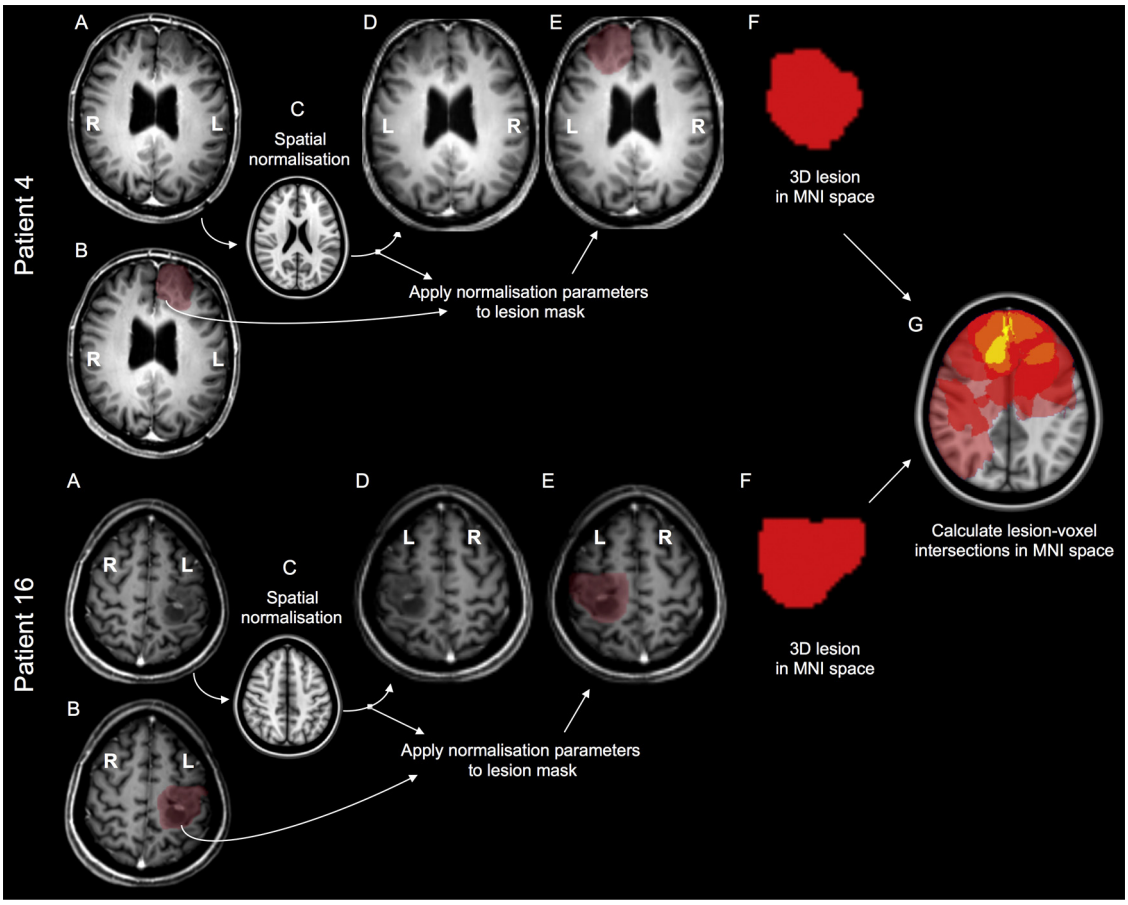

Fig. 1 Illustration of image processing for lesion mapping in a patient with a left frontopolar oligodendroglioma (top) and a patient with a left frontocentral oligodendroglioma (bottom). (A) Native image. (B) Native image with lesion mask superimposed. (C) Native image is non-linearly spatially normalized to the MNI template. (D) Non-linearly normalized image. (E) Image normalization parameters are applied to the segmented lesion to transform the lesion to MNI space (F). (G) Lesion-voxel intersection maps are generated in MNI space.

genu.This difference was statistically significant ($p = 0.03$). Lesion maps are shown with respect to the location of the probabilistic genu fibres in Fig. 5. There was no significant difference between GTCS and PS in terms of the number of lesion intersections with lobar, thalamic or striatal ROIs (Table 2). There was also no significant difference between patient groups with respect to the volume or percentage of tumours intersecting each ROI ($p > 0.05$). The mean tumour volume was 96,959.40 mm^3 (SD 78,883.34 mm^3) for patients with GTCS and 110,534.20 mm^3 (SD 102,652.65 mm^3) for patients with SPSPS. This difference was not statistically significant ($F = 0.11$, $p = 0.74$).

Discussion

Our structural MRI study underlined the central role of the genu of the corpus callosum for secondary generalization in

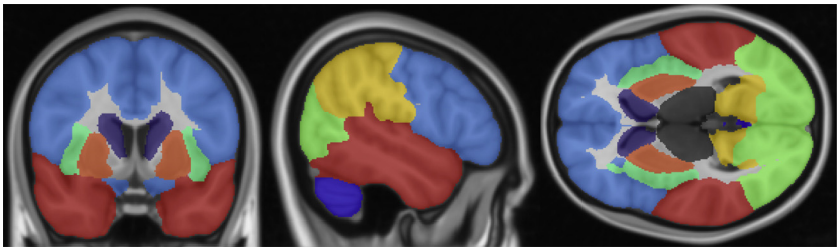

Fig. 2 A priori regions-of-interests (ROIs) obtained from the MNI probabilistic brain atlas. ROIs include frontal lobe (blue), parietal lobe (yellow), temporal lobe (red), occipital lobe (green), thalamus (black) and striatum (merged putamen (copper) and caudate (purple)). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

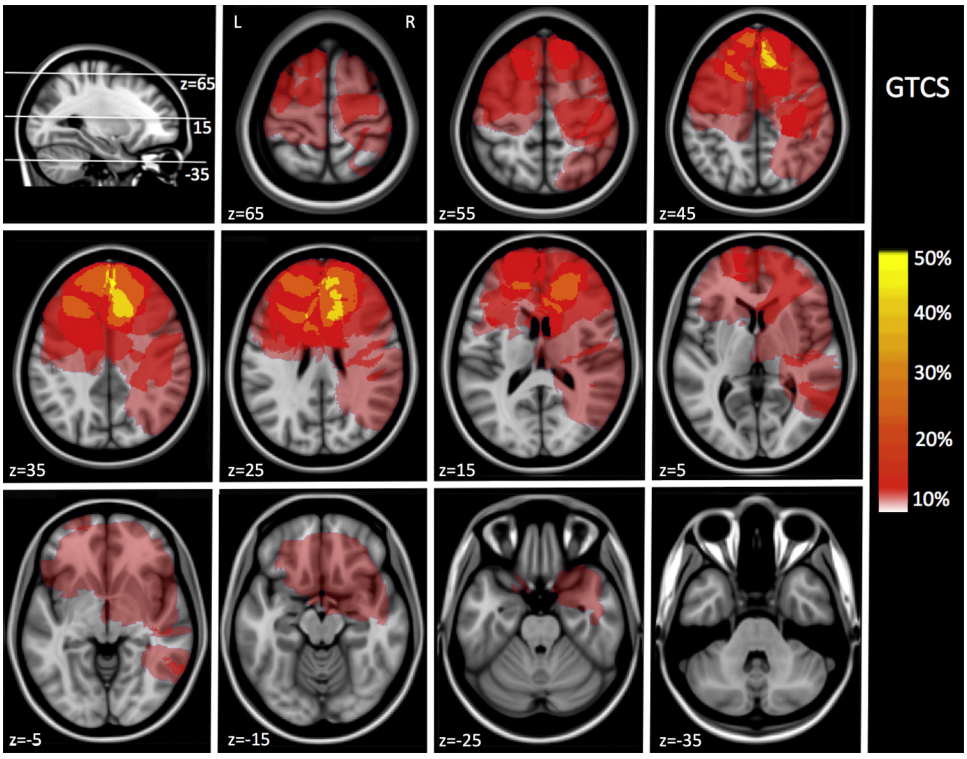

Fig. 3 Lesion mapping in patients with GTCS. Colours correspond to the number of times a voxel was intersected by a lesion and expressed as a percentage of patients. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

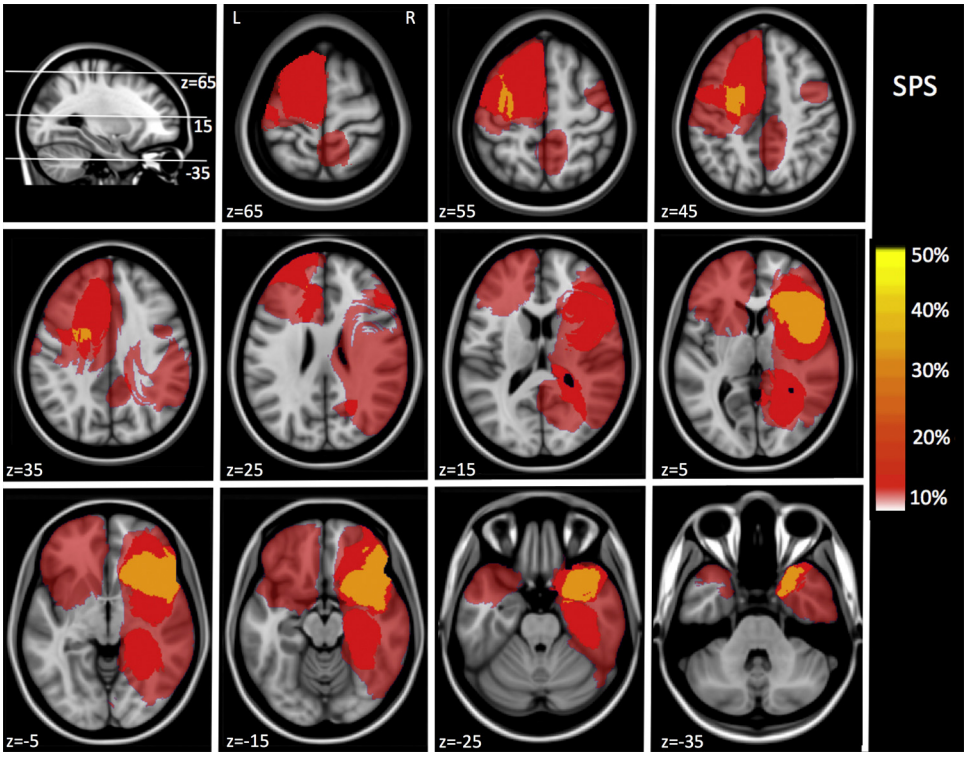

Fig. 4 Lesion mapping in patients with PS. Colours correspond to the number of times a voxel was intersected by a lesion and expressed as a percentage of patients. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

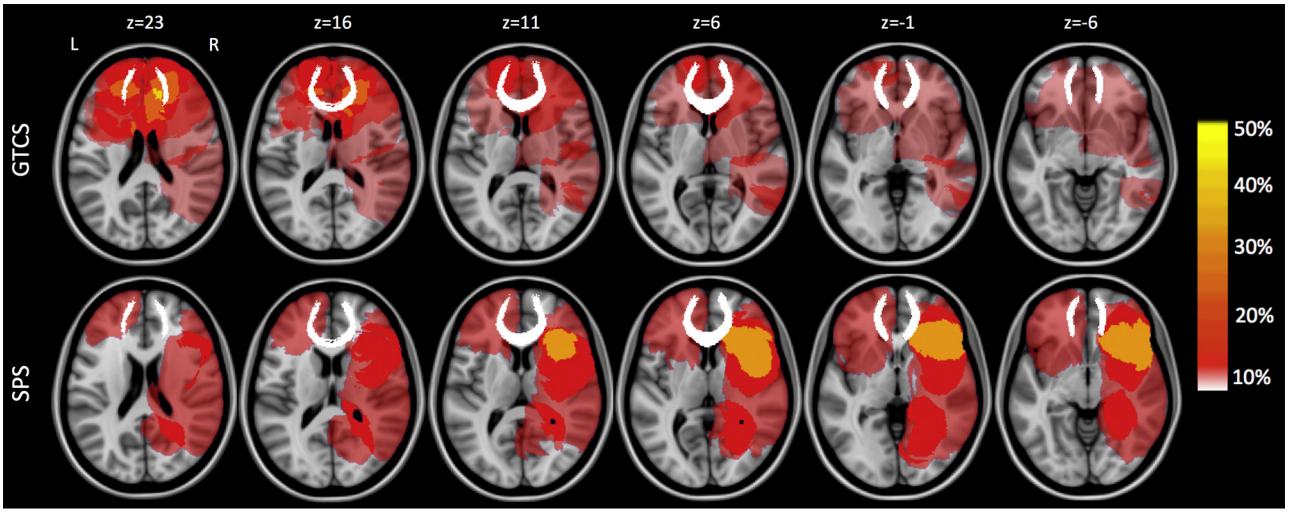

Fig. 5 Lesion maps for both patient groups at the level of the genu probabilistic ROI.

patients with tumours causing seizures. Using voxel-based lesion mapping of MRI images in a randomly selected cohort of patients with oligodendrogliomas, we demonstrated that lesions in cortical areas directly connected to the genu of the corpus callosum were significantly more likely to result in GTCS than lesions occupying brain regions not impinging on the genu of the corpus callosum.

Our results are consistent with observations on parasagittal lesions and secondary synchrony (Tukel and Jasper, 1952). They are also in keeping with previous studies indicating that anterior callosotomies can prevent secondary generalization (Van Wagenen and Herren, 1940; Tanriverdi et al., 2009). Taken together, these data suggest that the anterior portion of the callosum is crucial for generalization of tonic, tonic clonic, and atonic seizures. We can, of course, only speculate about the other parts of the corpus callosum, including mid- and posterior regions, and indeed other transcallosal pathways. The corpus callosum is only one of several structures connecting the two hemispheres, which also include the anterior commissure, posterior commissure, ventral and dorsal hippocampal commissures, the massa intermedia, and the fornix. Our data suggest these structures are of lesser importance for secondary generalization given that secondary generalization was less likely in patients with lesions connected to these more caudal structures.

Table 2 Fisher's exact (FE) categorical analysis of the number of lesions intersecting each ROI.

Region	Lesioned	SPS	GTCS	FE *p*
Frontal	Yes	9	10	1.00
	No	1	1	
Temporal	Yes	5	9	0.18
	No	5	2	
Parietal	Yes	8	5	0.18
	No	2	6	
Occipital	Yes	8	8	1.00
	No	2	3	
Striatum	Yes	4	4	1.00
	No	6	7	
Thalamus	Yes	7	9	0.64
	No	3	2	
Genu	Yes	2	8	***0.03***
	No	8	3	

Other studies also showed that temporal lobe oligodendrogliomas are associated with partial seizures (Chang et al., 2008). Our study additionally indicated that frontal lobe epilepsy caused by oligodendroglioma does not necessarily cause secondary generalized seizures unless the seizure onset zone is directly connected to fibres from the genu of the corpus callosum. This may explain why older studies (Ketz, 1974) and more recent studies failed to find an association of frontal oligodendrogliomas with GTCS (Whittle and Beaumont, 1995). Tumour size was not associated with GTCS. In fact, some tumours in patients with only simple partial seizure were very large involving more than one lobe, basal ganglia and thalamus.

Our findings indicate that the tumour localization is the most important factor to determine seizure semiology. Treatment strategies, both pharmocological and surgical aiming at suppressing seizure spread could be attractive options for the treatment of epilepsy.

Our findings have potential implications for the management of patients with oligodendrogliomas. Functional neurosurgery with a callosotomy could improve the outcome in patients with oligodendrogliomas and frequent generalized seizures. Furthermore, our results could inform and assist the work up of patients with refractory epilepsy without obvious structural abnormalities.

The brains of our patients were less distorted by the tumours even if they were large, because of the infiltrative growth of the oligodendrogliomas (Ketz, 1974). We tried to assist the delineation of the tumour on the T1 images but referring to the T2 images whenever necessary.

In our study, there were no other histological, genetic or biochemical factors affecting seizure spread, and all patients had histologically proven oligodendrogliomas. However, since it's first description by Bailey and Cushing (1926) in their famous treatise on brain tumours many new classifications and subtypes of oligodendrogliomas have been suggested. Oligodendrogliomas may show features of heterogeneity, and may include oligoastrocytoma or oligodendroglial glioblastoma multiforme. Unfortunately, due to such histopathologic variation the diagnosis is extremely difficult and is the source of bias in the studies on these tumours (Giannini et al., 2001). Variation in tumour grade may have introduced bias. Furthermore the 1p19q status may not only influence survival (Walker et al., 2005) and may also affect seizures (Huang et al., 2011). In our study the 1p19q was not tested in all patients but we did not find any obvious difference between GTCS and PS.

There are some methodological issues that warrant discussion. First, spatial normalization of lesioned brains presents a significant challenge (Andersen et al., 2010; Brett et al., 2001; Crinion et al., 2007), but is necessary for voxel-based lesion mapping. This approach has been performed frequently in studies determining the functions of damaged brain regions in patients with neurological disorders and large brain lesions (Karnath et al., 2004; Marchina et al., 2011; Matthews et al., 2013; Rinne et al., 2013; Rorden and Karnath, 2004). Non-linear normalization of patient images in the present study functioned sufficiently well insomuch that no major distortions were introduced during transformations, and oligodendrogliomas transferred to MNI space visually appeared representative of how they appeared in native space (see Fig. 1). It is important to be aware that non-linear normalization of large oligodendrogliomas may introduce subtle lesion distortions, but we do not expect that this will have affected the differences in lesion maps we have observed between our patient groups. Second, despite the opportunities afforded by lesion segmentation solely based on T1-weighted images (Sanjuan et al., 2013; Seghier et al., 2008), it is generally accepted that three dimensional MR volumes with T2 contrast including T2-weighted and fluid-attenuated inversion-recovery (FLAIR) images are superior for the identification of tumour borders. We did not have access to such data in our series, and there is therefore a possibility that we underestimated tumour extent given the contrast afforded by T1-weighted imaging. For voxel-based lesion mapping approaches, infarcts and tumours can be manually outlined on T2-weighted and FLAIR images that are co-registered with T1-weighted data that was acquired in the same scanning session. The spatial transformation parameters from each patient's T1-weighted data can be applied to the lesion segmented from the co-registered T2-weighted or FLAIR images to provide a more reliable representation of each oligodendroglioma. We are now prospectively acquiring multi-sequence T1-weighted, T2-weighted and FLAIR volumes that would permit such an analysis in patients with cavernomas. Third, we have assumed that the seizure onset zone for each patient overlapped with the localization of the delineated oligodedroglioma, which potentially may not be the case in some patients. Finally, as done in other studies, we would have performed voxel-based statistical comparisons between lesion maps if we had a significantly larger cohort of patients. However, such an analysis would be meaningless in the present study given the heterogeneous distribution of lesions in few patients. We therefore took the approach of determining whether or not, and the extent to which, lesions intersected specific brain regions and whether this is related to seizure generalization. Future studies on large cohorts of patients with oligodendrogliomas should employ voxel-based statistical analyses to calculated lesion maps and determine whether this approach also suggests the importance of callosal fibres for seizure generalization. Given the small numbers in our patient groups, and because of the aforementioned methodological issues, it is important to treat the data presented in this study as preliminary.

In conclusion, the present voxel-based lesion mapping study indicates that lesions in cortical areas connected to the genu of the corpus callosum are significantly more likely to result in GTCS than lesions in cortical areas not intersecting genu of the corpus callosum in patients with oligodendrogliomas. Further work is required to determine whether lesions affecting callosal fibres preferentially lead to GTCS in patients with other tumours.

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