

Cortical Gray–White Matter Blurring and Cognitive Morbidity in Focal Cortical Dysplasia

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Focal cortical dysplasia (FCD) is a malformation of cortical development that is associated with high rates of cognitive morbidity. However, the degree to which specific irregularities of dysplastic tissue directly impact cognition remains unknown. This study investigates the relationship between blurring of the cortical gray and white matter boundary on magnetic resonance imaging (MRI) and global cognitive abilities in FCD. Gray–white blurring (GWB) is quantified by sampling the non-normalized T_1 image intensity contrast above and below the gray and white matter interface along the cortical mantle. Spherical averaging is used to compare resulting GWB for patients with histopathologically verified FCD with matched controls. Whole-brain correlational analyses are used to investigate the relationship between blurring and general cognitive abilities, controlling for epilepsy duration. Results show that cognitive performance is reduced in patients with FCD relative to controls. Patients show increased GWB in bilateral temporal, parietal, and frontal regions. Furthermore, increased GWB in these regions is linearly related to decreased cognition and mediates group differences in cognitive performance. These findings demonstrate that GWB is a marker of reduced cognitive efficiency in FCD that can potentially be used to probe general and domain-specific cognitive functions in other neurological disorders.

Keywords: cognition, epilepsy, focal cortical dysplasia, gray and white matter blurring, quantitative MRI

Introduction

Early failures in cortical development can lead to a spectrum of abnormalities in cognition and behavior (Clowry et al. 2010). Focal cortical dysplasia (FCD) is a malformation of cortical development that is linked to disruption of early neuronal differentiation and migration (Crino and Eberwine 1997). Histopathologic features of FCD span a wide spectrum of cellular abnormalities and cortical architectural defects, such as immature small-diameter neurons, large dysmorphic neurons, undifferentiated balloon cells, and dyslamination (Blümcke et al. 2011). A common finding is increased numbers of “interstitial” neurons in the superficial white matter that are suggestive of either disrupted migration or a failure of subplate cell death (Thom et al. 2001). Given this wide spectrum of defects, it is not surprising to find cognitive consequences of FCD (Duchowny 2009); however, little is known about the degree to which specific features of FCD might disrupt the efficiency of cognitive networks.

The most commonly appreciated consequence of FCD is seizures. Dysplastic lesions occur in more than a quarter of adult patients with medically refractory focal epilepsy (Lerner et al. 2009). Furthermore, dysplasia is the most frequent histopathologic finding in surgical specimens removed from patients with

cryptogenic epilepsy (Chapman et al. 2005; Wang et al. 2013); thus, dysplastic lesions can be subtle, easily missed with clinical magnetic resonance imaging (MRI) sequences, and potentially present in even “normal” appearing brains. Animal models indicate that dysplastic lesions contribute to cognitive impairment, independent of seizures (Lucas et al. 2011). This raises the possibility that dysplasia in humans may directly contribute to cognitive burden, even in patients with normal MRI and independent of chronic seizure activity.

Advances in quantitative MRI (qMRI) are improving detection of subtle, visually elusive, FCD lesions (Besson et al. 2008; Bernasconi et al. 2011; Thesen et al. 2011). The development of qMRI metrics that are sensitive and specific to FCD creates the opportunity to directly investigate their linear relationship to cognitive indices. One of the most common MRI findings in FCD is blurring of the gray and white matter boundary (Mühlebner et al. 2012). Optimal detection of dysplastic lesions is achieved with a gray–white contrast ratio score that samples the degree of blurring at each point on the cortical mantle (Thesen et al. 2011). This metric is directly related to verbal performance in healthy controls (Blackmon et al. 2011). Taken together, such findings suggest that gray–white contrast is a qMRI metric that can be used both to detect subtle dysplastic regions and to probe the integrity of cognitive functions.

In the current study, we use the General Abilities Index (GAI) from the Wechsler Adult Intelligence Scale (Tulsky et al. 2001) to test the hypothesis that GAI scores are reduced in patients with FCD relative to healthy controls, and that increased gray–white blurring (GWB) in temporal, parietal, and frontal regions mediates this relationship. Furthermore, we test the hypothesis that the relationship between GWB and cognitive performance is independent of epilepsy duration in patients. In summary, this study aims to validate GWB as an *in vivo* marker of reduced cognitive efficiency that can be linked to histopathologically diagnosed FCD through the demonstration of group differences in both GWB and GAI scores.

Materials and Methods

Participants

This study was approved by the IRB of New York University. All patients signed consent to participate. Participants with FCD were identified from a consecutive series of surgically treated patients at the NYU Comprehensive Epilepsy Center from 2007 to 2013. Participants were selected for this study if they met the following criteria: (1) Acquisition of a research MRI scan prior to surgery; (2) histopathologic evidence for FCD Type I (Ia or Ib), Type II (IIa or IIb), or Type IIIa from tissue extracted during epilepsy surgery (Blümcke et al. 2011); (3) acquisition of a neuropsychologic test battery prior to surgery; (4) at least 16 years of age (to fit within the normative sample range for the Wechsler Adult Intelligence Scale III and IV); and (4) the absence of any non-FCD lesions, with the exception of hippocampal sclerosis (Type

IIIa). The latter criteria excluded 2 patients with glial–neuronal tumors, one patient with a cavernous angioma and another patient with evidence of an old infarct. The result was 20 patients: 10 who underwent left hemisphere resective surgery and 10 who underwent right hemisphere resective surgery. Subjects were classified as MRI-positive or -negative based on visual review of all available presurgical clinical scans by R.K. We recorded age of epilepsy onset and duration of epilepsy (Table 1).

All controls signed consent to participate. Controls were recruited from the community by advertisement with the following criteria: (1) No history of psychiatric disorders; (2) no history of medical disorders affecting the nervous system; (3) no history of psychotropic or neurologic medications; and (4) no MRI contraindications. The MRI scanner and scan parameters were identical between patients and controls. Following consent and MRI acquisition, controls were administered a comprehensive neuropsychologic testing battery to rule out cognitive disorders. From this larger control database, a group of 20 healthy controls were matched to patients for the current study on the basis of age (± 5 years), gender, and handedness (Table 1).

MR Image Acquisition

All patients and controls completed a specialized T_1 -weighted magnetization-prepared rapid acquisition with gradient echo (MPRAGE) MRI scan sequence on an Allegra 3-T dedicated research scanner. The acquired images included a 3-plane localizer and a T_1 -weighted volume pulse sequence (time echo = 3.25 ms, time repetition = 2530 ms, time to inversion = 1100 ms, flip angle = 7° field of view = 256 mm, matrix = 256x256, voxel size = $1 \times 1 \times 1.3$ mm, scan time: 8:07 min). The image acquisition parameters were optimized to increase the gray–white matter contrast in the scanned images. Postprocessing of the acquired images included corrections for nonlinear warping resulting from nonuniform fields generated by gradient coils. The T_1 -weighted image was reoriented into a common space, roughly similar to alignment based on the anterior commissure–posterior commissure line. The images were further refined and normalized using the FreeSurfer 5.1 software package (<http://surfer.nmr.mgh.harvard.edu/>).

Surface Reconstruction

To recreate the morphological characteristics of the cerebral cortex using the volumetric scans, the procedure described in Fischl et al. (1999) was followed. This procedure roughly involves: (1) Segmentation of the white matter, (2) tessellation of the gray–white matter boundary, (3) inflation of the folded surface, and (4) correction of topological defects. Once the surface was reconstructed, it was further refined by classifying all white matter voxels in the MRI volume to create the gray–white matter boundary. The gray–white matter junction was delineated up to submillimeter accuracy by further refining the white matter surface. After refining the gray–white matter junction, the pial surface was located by deforming the surface outward. The surface reconstruction procedure was followed by a registration process that involved the alignment of sulcal and gyral features for each subject's brain by morphing each reconstructed surface to an average spherical

Table 1
Characteristics of the whole sample

	FCD patients (N = 20)		Healthy controls (N = 20)	
	Min–Max	Mean (SD)	Min–Max	Mean (SD)
Sex	5 males/15 females		5 males/15 females	
Handedness	1 left-hander		1 left-hander	
Age	17–53	32 (9.6)	19–52	32.9 (9.1)
Years of education	10–19	14.5 (2.7) ^a	12–20	16.3 (2)
Epilepsy onset age	3–35	13.5 (8.8)		
Epilepsy duration	2–41	18.7 (11)		

FCD, focal cortical dysplasia; TL, temporal lobe; FL, frontal lobe; PL, parietal lobe; OL, occipital lobe; MRI+, visible lesion on clinical MRI; MRI–, clinical MRI interpreted as normal.

^aFCD group mean years of education is significantly lower than control mean at $P < 0.05$.

representation that accurately matches the cortical locations among individual subjects while minimizing metric distortion at each location (Fischl and Dale 2000).

Morphometric Feature Extraction: Gray and White Matter Blurring

GWB was estimated by calculating the non-normalized T_1 image intensity contrast ($[\text{gray} - \text{white}] / [\text{gray} + \text{white}]$) at 0.5 mm above versus below the gray–white interface with trilinear interpolation of the images (Fig. 1). Resulting GWB values ranged from -1 to 0 , with values closer to zero indicating a higher degree of blurring at the gray–white matter junction.

Cognitive Testing

General cognitive abilities were assessed with the Wechsler Adult Intelligence Scale—Third Edition and Fourth Edition (WAIS-III and WAIS-IV). The GAI can be derived from both the Third and Fourth Edition of the WAIS. The GAI is an optional index score that provides an estimate of general intellectual ability with reduced emphasis on working memory and processing speed relative to the Full-Scale IQ score. This makes the GAI less sensitive to clinically fluctuating factors, such as mood, medications, and recent seizures (Tulsky et al. 2001;

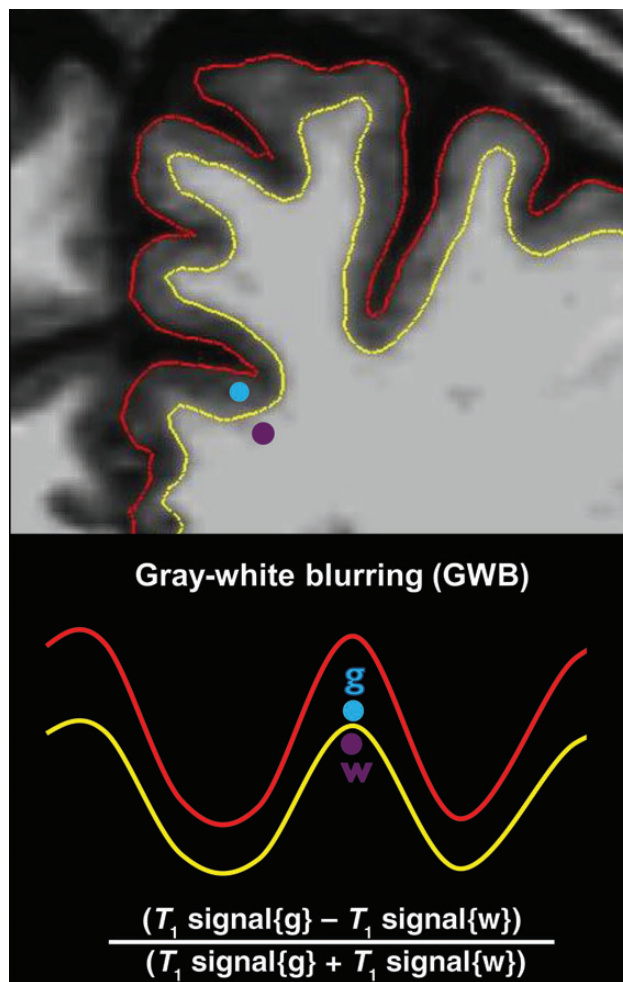


Figure 1. Computing GWB: Sampling points on T_1 -weighted MPRAGE image with gray–white (GW) junction surface (yellow line) and pial surface (red line). The blue dot shows the sampling location of the gray matter intensity value at 0.5 mm into the gray matter relative to the GW junction. The purple dot shows the sampling location of the white matter intensity value at 0.5 mm into the white matter relative to the GW junction. Sampling is repeated at each vertex along the GW junction.

Iverson et al. 2006). Demographically adjusted GAI scores can be derived by comparing individual raw scores to age-, gender-, education-, and ethnicity-matched cohorts from the large standardization sample. These scores are available from the tests' publishers and provide good overall diagnostic accuracy in neuropsychologic assessments (Taylor and Heaton 2001). Given significant differences in educational attainment between our patient and control sample (Table 1), these demographically adjusted *T*-scores (mean = 50, SD = 10) were used in all analyses.

Pathology

All specimens were evaluated at the Department of Pathology, NYU Langone Medical Center following standard clinical protocols. Each specimen was evaluated macroscopically. Cortical specimens were sectioned perpendicular to the cortical surface and formalin-fixed and paraffin-embedded following standard clinical laboratory protocols. Five-micrometer sections were cut on positively charged slides, stained with hematoxylin and eosin (H&E), and evaluated by a board certified neuropathologist (M.S.). Immunohistochemistry for NeuN, neurofilament, synaptophysin, and glial fibrillary acidic protein (GFAP) was performed on selected sections showing FCD following standard clinical protocols. All participants were diagnosed with FCD based on the International League Against Epilepsy (ILAE) classification scheme (Blümcke et al. 2011). Type I indicates radial (Type Ia) and/or tangential (Type Ib) cortical layering defects, immature small-diameter neurons, and increased numbers of heterotopic neurons in the subjacent white matter. Type II indicates more severe cortical lamination defects and large, dysmorphic neurons (Type IIa), and balloon cells (Type IIb), accompanied by heterotopic neurons in the subjacent white matter. Type IIIa indicates the presence of both cortical lamination abnormalities and mesial temporal sclerosis. A semiquantitative analysis of interstitial white matter neuron (IWMN) count was performed and was graded based on the average number of NeuN-positive neurons per high power field (HPF) over 10 HPF of the white matter. It was graded as mild (<5/HPF), moderate (5–10/HPF), and severe (>10/HPF) neurons/HPF at ×400 magnification. Histopathologic characterization of each patient is presented in Table 2.

Statistical Analyses

T-tests were used to test for group differences in demographically adjusted GAI scores. Following Freesurfer v5.1 reconstruction of each

MRI T_1 scan, surface maps were smoothed with a Gaussian kernel (10 mm full-width at half-maximum) and averaged across participants using spherical averaging (Fischl et al. 1999). For each hemisphere, a general linear model was used to estimate vertex-wise group differences in GWB and the linear effects of GWB on GAI scores. We controlled for family-wise error rate by means of Monte Carlo (Hayasaka and Nichols 2003; Hagler et al. 2006). Data were tested against an empirical null distribution of maximum cluster size across 10 000 iterations synthesized with an initial cluster threshold of $P < 0.05$, yielding significant clusters corrected for multiple comparisons across all vertices.

To test whether GWB differences were more pronounced in the region that was ultimately resected and histopathologically evaluated, we manually traced the resection zone on the postsurgical MRI using FSLview, resulting in a resection mask for each 18/20 patients (in 2 patients a postsurgical scan was not obtainable). A rigid-body transformation was used to coregister this resection mask to the presurgical T_1 -weighted volume. The resection mask was then transformed to surface space and used to extract average GWB values from within and outside the resection zone for each patient. Each patient was then case-matched to a control participant by age (± 6 years) and gender, and the resection mask for that patient was overlaid on the case-matched control brain in surface space to extract average GWB values from within and outside the mask region. Two paired *t*-tests were performed to compare average GWB values between patients and their case-matched controls, both (1) within and (2) outside the resection mask area.

To determine whether group differences in GWB mediated differences in GAI scores, we extracted average GWB values from the regions that were statistically different between patients and controls in the whole-brain vertex-wise analyses. Nested regression models were used to determine whether group differences in GAI scores mediated by differences in GWB. Specifically, we tested whether the significant difference in GAI scores between patients and controls was reduced or no longer significant when GWB scores were added as an independent variable in the regression model.

Results

Are General Cognitive Abilities Reduced in Patients with FCD Relative to Healthy Controls?

In the FCD group, GAI scores ranged from 28 to 59 (mean = 44.85, SD = 8.5), and in the healthy control group, GAI scores ranged from 31 to 75 (mean = 55.9, SD = 12.02). Overall, patients with FCD had significantly lower average GAI scores than controls [$t_{(38)} = -3.35$; $P = 0.002$; Fig. 2]. GAI scores were reduced in patients with left hemisphere seizure onset/surgery [$t_{(28)} = -2.84$; $P = 0.008$] and right hemisphere seizure onset/surgery [$t_{(28)} = -2.32$; $P = 0.028$], compared with controls. Within the FCD group, there were no correlations between GAI scores and age of onset ($r = 0.38$, $P = 0.096$), or epilepsy duration ($r = -0.39$, $P = 0.147$).

Is GWB Increased in Patients with FCD Relative to Controls?

Group differences (FCD vs. healthy controls) in GWB were analyzed on a vertex-by-vertex basis across both hemispheres, separately. Increased GWB was observed in FCD patients relative to controls in multiple cortical regions, including the lateral temporal, inferior parietal, and superior frontal lobes bilaterally, after correction for multiple comparisons. There were no regions where GWB was higher in healthy controls (Fig. 3).

Paired *t*-tests comparing average GWB values extracted from within the resected region in each patient, relative to average GWB values from the same brain regions in case-matched controls, revealed a significant difference: $t_{(17)} = 2.3$; $P = 0.034$,

Table 2

Characteristics of FCD sample

	FCD type	IWMN count	MRI-visible lesion	Hemisphere	Lobe
1	IA	Mild	MRI+	Right	TL
2	IA	Moderate	MRI-	Right	TL
3	IA	Moderate	MRI+	Left	TL
4	IA	Mild	MRI+	Left	TL
5	IIB	Moderate	MRI+	Right	FL
6	IA	Moderate	MRI-	Left	TL
7	IIB	Mild	MRI-	Right	FL
8	IB	Mild	MRI-	Right	PL
9	IIIA	Moderate	MRI-	Right	TL
10	IA	Moderate	MRI-	Left	TL
11	IA	Moderate	MRI+	Left	TL
12	IA	Moderate	MRI-	Left	TL
13	IIB	Moderate	MRI-	Right	TL
14	IA	Moderate	MRI-	Left	TL + FL
15	IIIA	Mild	MRI-	Right	TL
16	IA	Mild	MRI-	Right	FL
17	IIIA	Moderate	MRI-	Right	TL
18	IA	Moderate	MRI-	Left	TL
19	IIA	Unavailable	MRI-	Left	OL
20	IIA	Severe	MRI+	Left	FL

Note: FCD classification based on International League Against Epilepsy 2011 Classification Scheme.

FCD, focal cortical dysplasia; IWMN, interstitial white matter neurons; AEDS, antiepileptic medications; MRI+, visible lesion on clinical MRI scans; MRI-, no visible lesion on clinical MRI scans; TL, temporal lobe; FL, frontal lobe; PL, parietal lobe; OL, occipital lobe.

with higher GWB in the resected region of patients compared with a corresponding region in controls. Outside the resection zone, patients showed a trend toward higher average GWB: $t_{(17)} = 1.86$; $P = 0.081$.

Are There Vertex-Wise Associations Between GWB and GAI Scores in Both the Patient and the Healthy Control Group?

Whole-brain, vertex-based analyses of correlations between GWB and demographically adjusted GAI scores revealed widespread negative correlations in both the control group and the FCD group, after correction for multiple comparisons (Fig. 4A, B). Significant correlations spanned both hemispheres, including gyral and sulcal regions. Furthermore, although all tests were two-tailed, results were unidirectional in that increased blurring was consistently associated with decreased performance in both patients and controls. In the FCD group, regions

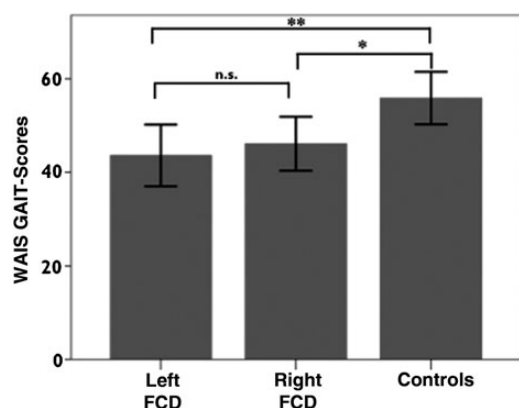


Figure 2. Bar graph depicting mean demographically adjusted GAI scores for individuals with right and left hemisphere FCD lesions and healthy controls. Error bars represent 95% confidence intervals. *: significant at $P < 0.05$; **: significant at $P < 0.001$; n.s.: nonsignificant.

showing the strongest correlations included medial and lateral frontal lobes, anterior cingulate, superior and inferior parietal, superior temporal, and calcarine cortex. In controls, significant regions spanned the frontal lobes, anterior cingulate, inferior and superior parietal, and superior temporal cortex.

Is the Association Between GWB and GAI Scores Independent of Epilepsy Duration?

In the FCD group, epilepsy duration was entered as a nuisance variable in the whole-brain, vertex-wise analyses. Significant negative correlations persisted between increased GWB and decreased GAI scores across bilateral frontal lobes and anterior cingulate, after correction for multiple comparisons (Fig. 4C).

Does GWB Mediate Group Differences in General Cognitive Abilities?

Given the significant group difference in GAI scores between FCD patients and controls, as well as a significant difference in GWB in specific cortical regions, we further tested whether GWB from these regions was correlated with the GAI, after controlling for group, in order to formally test for mediation effects (Baron and Kenny 1986). GWB values were extracted from regions that significantly differed between patients and controls and averaged separately for the left and right hemispheres; the resulting averages were then correlated with GAI scores, controlling for group (see scatterplots in Fig. 3A, C for visualization of the relationship between GWB in these clusters and GAI scores). GAI scores were significantly correlated with average left ($\beta = -0.53$; $t = -3.86$; $P = 0.000$) and right ($\beta = -0.59$; $t = -4.16$; $P = 0.000$) hemisphere GWB values from these clusters, after controlling for group. Furthermore, the relationship between group and GAI scores was no longer significant after controlling for GWB scores in both the left ($\beta = 0.23$; $t = 1.63$; $P = 0.112$) and the right ($\beta = 0.17$; $t = 1.19$; $P = 0.242$) hemispheres, indicating that the impact of FCD on cognitive performance is indirectly mediated by GWB in

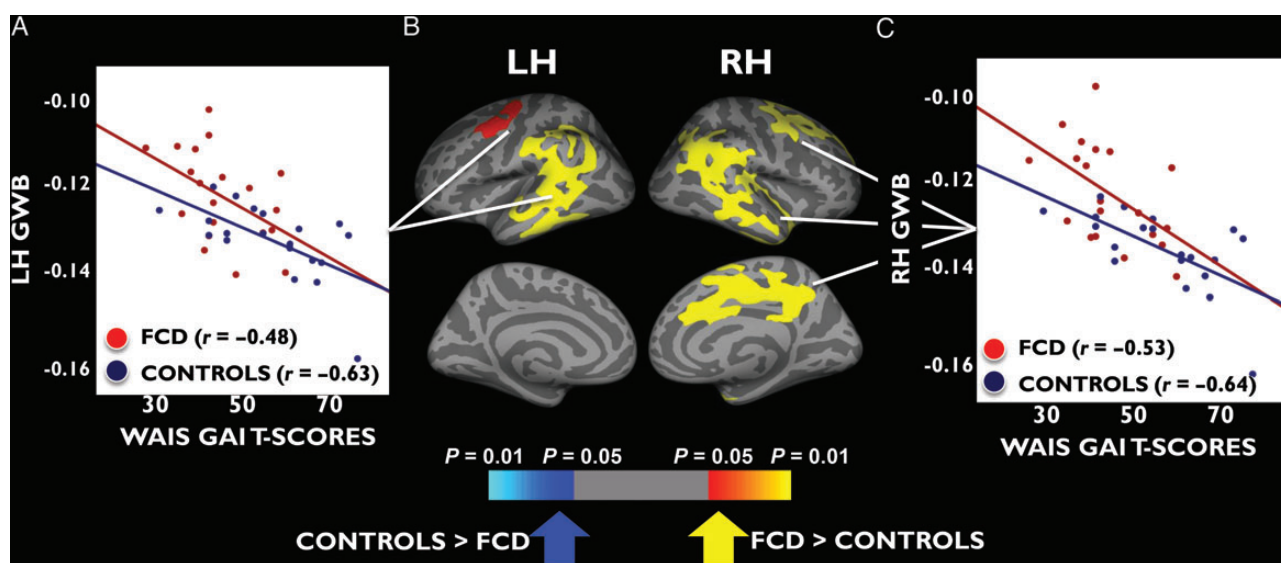


Figure 3. The results of whole-brain, vertex-based comparisons of differences in mean GWB between FCD patient and controls are depicted on an inflated left and right cortical surface (B). Areas in red and yellow show clusters of greater blurring in FCD patients, after correction for multiple comparisons, in superior temporal, inferior parietal, and superior frontal regions of the right and left hemispheres. The absence of blue clusters demonstrates that there were no regions where controls showed greater blurring than patients. Scatterplots depict the relationship between average GWB scores for each individual patient (red dots) and control (blue dots) from (A) the left hemisphere clusters and (C) right hemisphere clusters plotted against GAI scores.

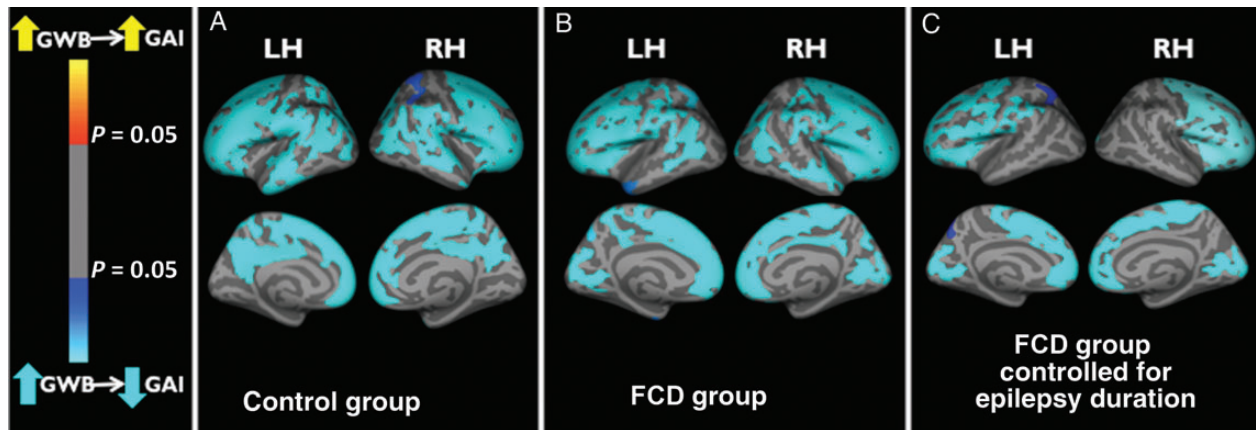


Figure 4. The results of whole-brain, vertex-based correlations between GWB and GAI scores (corrected for multiple comparisons) are depicted on an inflated surface for (A) the healthy control group; (B) the FCD group, and (C) the FCD group after partialing out epilepsy duration. Blue clusters represent regions where there was a significant inverse relationship between GWB and GAI scores, indicating increased blurring associated with decreased cognition. The absence of any red or yellow clusters indicates that there were no regions where increased GWB was associated with increased GAI scores.

lateral temporal, inferior parietal, and superior frontal regions, bilaterally.

Discussion

Blurring of the cortical gray–white matter junction is a distinctive MRI and histopathologic feature of FCD (Mühlebner et al. 2012). Using a qMRI measure of GWB, we found a relationship between the degree of GWB and cognitive dysfunction in individuals with histopathologically verified FCD. Patients with both right and left hemisphere FCD lesions showed reduced cognitive abilities relative to matched controls. Furthermore, in whole-brain vertex-wise analyses, there was evidence of increased blurring in patients relative to controls in lateral temporal, inferior parietal, and superior frontal regions bilaterally, which is consistent with the predominance of temporal and frontal lobe dysplasia cases in the current sample. A more specific analysis of GWB values, averaged across the resection area of each patient, revealed greater blurring compared with the corresponding regions in case-matched controls. This demonstrates that although there were several regions where GWB was increased at the group level in FCD patients relative to controls, individual elevations in GWB values were most concentrated in the regions that were surgically resected and sampled for histopathologic evaluation.

Results from whole-brain correlational analyses between GWB and GAI scores revealed a positive relationship between GWB and general cognitive abilities across widespread temporal, frontal, and parietal regions in both FCD patients and controls. This relationship was unidirectional, with increased blurring invariably associated with decreased cognitive abilities in both groups. The relationship between increased blurring and reduced cognition was independent of epilepsy duration, which demonstrates that they are not just the shared secondary effects of chronic seizures. Finally, blurring in lateral temporal, inferior parietal, and superior frontal regions statistically mediated the relationship between FCD and reduced cognitive performance. Taken together, results promote GWB as a qMRI marker for cognitive morbidity in FCD.

Increased GWB in the FCD group relative to healthy controls is particularly notable given the absence of a visible lesion on

clinical MRI sequences in 70% (14/20) of the sample. In these cases, the surgical resection was based on identification of the seizure onset zone with intracranial electroencephalography (Noe et al. 2013). Histopathologic evaluation of the resected tissue revealed the presence of radial or tangential dyslamination defects (FCD Type Ia or Ib, respectively), dysmorphic or immature neurons (FCD Type IIa), and/or balloon cells (FCD Type IIb), despite the absence of a visible lesion on imaging. Additionally, in all cases, there was evidence of mildly to moderately increased heterotopic/IWMNs. This is consistent with prior studies that report high rates of FCD in resective surgery tissue samples from patients with cryptogenic, or imaging-negative, epilepsy (Wang et al. 2013). These findings demonstrate that GWB is sensitive to FCD-associated features that may not be visibly appreciable on MRI, yet still disruptive to cognitive networks.

Which FCD-Associated Tissue Characteristics Might Impact MRI Signal Abnormalities at the Cortical Gray–White Junction?

Although the lack of coregistration between tissue samples and MRI precludes a direct one-to-one correspondence, current findings of increased GWB values averaged across the entire resection zone can be used to generate hypotheses about FCD tissue features that might contribute to elevated GWB in individual patients. FCD features, such as increased neuronal density and decreased neuropil (Blümcke et al. 2011), could contribute to a higher GWB ratio by increasing the gray matter signal. Axonal density near the gray–white junction can impact T_1 values by influencing the amount of interstitial water content; more tightly bundled axons would have shorter T_1 and would therefore appear brighter (Paus et al. 2001). Therefore, reduced axonal density can result in decreased white matter signal intensity on T_1 and increased GWB, as has been shown with prior combined MRI–histopathologic studies in mesial temporal sclerosis (Garbelli et al. 2012) and FCD (Shepherd et al. 2013) patients.

Another potential contributing factor is the presence of increased IWMNs just below the cortical layer VI (Fig. 5). These supernumerary or heterotopic neurons, termed IWMNs (Ramon Y Cajal 1911), thinly populate the superficial white

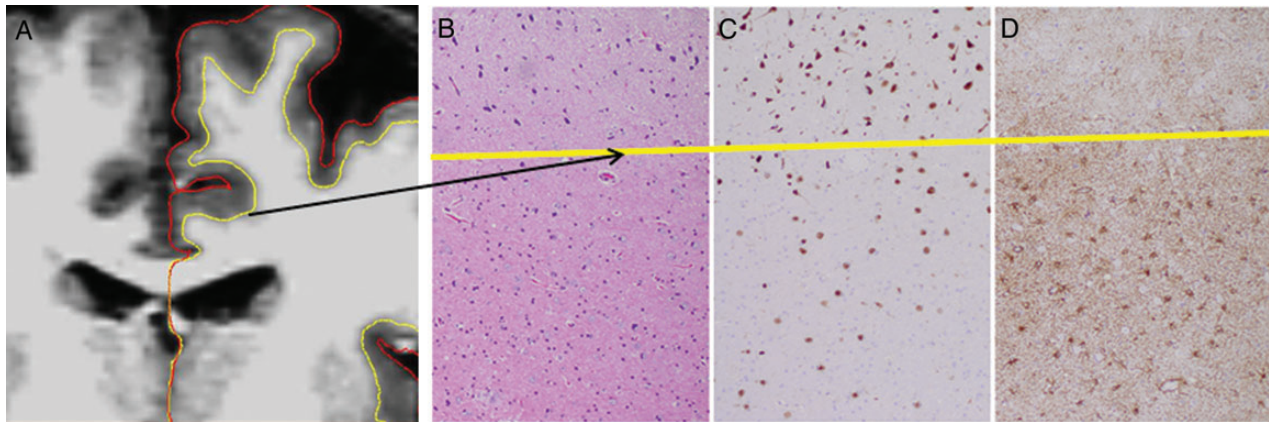


Figure 5. Histologic and immunohistochemical evaluation of the gray–white matter junction in a 30-year-old participant with FCD shown on MRI (A) in the left anterior cingulate. Yellow line shows the border between the cortex (above the line) and white matter (below the line). Hematoxylin and eosin (H&E) section (B) shows increased cellularity of the white matter. Immunohistochemistry for neuronal marker NeuN (C) shows numerous neurons in the white matter. An increased number of white matter neurons is associated with striking reactive gliosis, which is highlighted by immunohistochemistry for GFAP (D). Original magnification $\times 100$.

matter of healthy adult brains (Kostovic and Rakic 1980; Hardiman et al. 1988; Suárez-Solá et al. 2009; García-Marín et al. 2010). They are in highest concentration proximal to cortical layer VI with a gradual decrease in density deeper into the white matter (Kostovic and Rakic 1980). Although considered to be a normal variant that can subtly blur the gray-to-white matter transition in healthy controls (Rojiani et al. 1996; Judaš, Sedmak, Pletikos 2010; Judaš, Sedmak, Pletikos, et al. 2010), an increase in IWMN density has long been linked to pathology (Ranke 1910).

FCD is associated with pathologically elevated IWMNs (Matsuda et al. 2001; Tassi et al. 2002; Colombo et al. 2003; Krsek et al. 2008), evident across all ILAE FCD subtypes (Mühlebner et al. 2012). Animal models and human postmortem histology suggest that IWMNs may be cortical projection neurons disrupted during radial migration from the ventricular zone to the cortical plate (Rakic 1988; Chevassus-au-Louis and Represa 1999), due to genetic or environmental factors (reviewed in Kwan et al. 2012) and thus arrested in a heterotopic position outside the six-layer cortex. Another possibility is that they are remnants of the embryonic subplate (Kostovic and Rakic 1980, 1990; Chun and Shatz 1989) that failed to undergo programmed cell death (Luhmann et al. 2009). Evidence for the latter includes the presence of “dark” interstitial neurons that appear to have been arrested in the process of disintegration (Kostovic and Rakic 1980). In either case, the extent to which IWMNs facilitate or interfere with functional networks is the subject of debate (Clowry et al. 2010; Kwan et al. 2012; Judaš et al. 2013).

Could FCD-Associated Tissue Features Be Disruptive to Cognitive Networks?

There is a high rate of cognitive impairment in FCD, particularly in children, ranging from 50% to 80% (Rossi et al. 1996; Chassoux et al. 2000; Korman et al. 2013). Specific attention to FCD subtypes reveals that there may be a greater risk for cognitive impairment in FCD Type I (Krsek et al. 2008), although this is not consistently observed (Widdess-Walsh et al. 2005; Korman et al. 2013). Rates of cognitive impairment in adults with FCD are not as high, but still represent a significant risk for cognitive comorbidity, with cognitive deficits or previously

delayed development present in 22–50% of adult cases (Lawson et al. 2005).

Variation in neuropsychologic profiles can be related to the age of epilepsy onset, FCD lesion location, and lesion extent (Korman et al. 2013); however, it is possible that specific histopathologic features may be particularly disruptive to cognitive functions. There is individual variability in the degree to which FCD lesions are activated on fMRI motor and cognitive localizer tasks (Danckert et al. 2007), even within the same FCD subtype (Barba et al. 2012). One feature that appears to reliably predict functional silence is the presence of balloon cells (Danckert et al. 2007), which may facilitate reorganization of function to adjacent tissue and relative preservation of cognitive functions in FCD Type IIb.

Although reduced axonal density or hypomyelination is well established as factors that impair cognitive efficiency (Fjell and Walhovd 2010), the degree to which IWMNs interfere with cognitive or behavioral networks is unclear. These neurons have morphological features similar to cortical neurons (Kostovic and Rakic 1980; Meyer et al. 1992; García-Marín et al. 2010) and express a variety of neurochemicals (Meyer et al. 1992; Uylings and Delalle 1997; Finney et al. 1998; Suárez-Solá et al. 2009; Judaš et al. 2010); however, their dendritic branching pattern is altered (Chevassus-au-Louis and Represa 1999), and they often form aberrant networks with normally unconnected structures (Chevassus-Au-Louis et al. 1998). This may explain the lowered seizure threshold in individuals with FCD, but could these characteristics also directly contribute to disruption of cognitive and behavioral networks?

IWMNs are abnormally increased in a variety of developmental and psychiatric disorders such as schizophrenia (Akbarian et al. 1993; Eastwood and Harrison 2003; Connor et al. 2009; Yang et al. 2011), bipolar disorder, (Connor et al. 2009), and autism (Bailey et al. 1998; Wegiel et al. 2010). Furthermore, MRI signal abnormalities at the gray–white junction have been investigated in schizophrenia, with increased GWB localized to the frontal and temporal lobes (Kong et al. 2012), a finding that is consistent with prior reports of increased white matter neuron density in these regions in people with schizophrenia (Akbarian et al. 1993; Connor et al. 2009; Yang et al. 2011). This suggests that a relative increase in IWMNs proximal

to the gray white junction may contribute to increased GWB and behavioral dysfunction; however, direct correspondence between MRI signal and pathology is still needed to confirm this association.

How Do We Explain the Strong Relationship Between GWB and GAI Scores in Healthy Controls?

Similar to patients with FCD, increased blurring is consistently related to decreased performance across widespread temporal, frontal, and parietal regions in healthy controls. The unidirectional nature of this relationship is similar to what we found in a previous study of gray–white matter contrast and verbal cognition in healthy controls (Blackmon et al. 2011). Results in that study were selective to left hemisphere perisylvian regions, which was in line with the verbal nature of the cognitive tasks. The more widespread, bilateral results in the current study are remarkably consistent with neuroanatomical regions implicated in meta-analyses of general (visuospatial and verbal) intellectual abilities (Jung and Haier 2007). However, such strong and widespread effects may appear counterintuitive considering the presumed absence of FCD in the control sample.

One possibility is that there is a continuum of axonal and IWMN density at the gray–white junction from controls to patients, with an unclear threshold for distinguishing healthy from pathologic tissue. The distribution of IWMN in the superficial white matter of the temporal lobe in healthy control subjects ranges from 1 to 5 neurons/mm² (mean = 2.35 ± 0.96 neurons/mm²) (Rojiani et al. 1996), which overlaps with the distribution from the same region in temporal lobe epilepsy resection tissue (mean = 4.11 ± 1.86 neurons/mm²) (Emery et al. 1997). Thus, although IWMN counts are higher in temporal lobe epilepsy than in controls, the overlapping distribution suggests a continuum from normal to pathologic. Comparisons between healthy control and epilepsy tissue have shown similar overlapping distributions of other histologic features, such as laminar disorganization (Kasper et al. 1999) and perivascular glial satellitosis (Arai et al. 2003). This suggests that many dysplastic features, which were historically grouped under the category of “microdysgenesis” (Kasper et al. 2009), are also found in normal brains, which has rendered them more controversial for use in pathologic classification. The quantitative degree, rather than mere presence, of abnormalities becomes an important consideration; however, “degree” is often difficult to assess with limited tissue samples on histopathologic evaluations. This makes the link between qMRI and histology even more critical, in that MRI allows for whole-brain, quantitative comparisons with controls.

A recent twin study utilizing the Vietnam Era Twin Study of Aging (VETSA) sample found significant genetic influence on cortical gray and white matter contrast, with heritability estimates ranging from 0.29 to 0.66 (Panizzon et al. 2012). These heritability estimates are similar in magnitude to those reported for cortical thickness (Kremen et al. 2010), although the genetic and environmental determinants of gray–white matter contrast were found to be largely independent of those that influence cortical thickness. The association between GWB and FCD suggests that GWB may be used as an endophenotypic metric in investigations of genetic contributions to cortical maturation and migration failures. Currently, no *in vivo* MRI biomarker for variations in early migrational

processes exists. The results from our study provide support for GWB to serve such a role and to ultimately link subtle variations in cortical development to individual differences in behavior and cognition from the normal to the pathologic spectrum.

Limitations

One important limitation of the current study is that diagnosis was obtained retrospectively from routine clinical postsurgical pathology evaluations. Pathology was not directly compared in side-by-side manner with imaging at the time of specimen processing, which is particularly limiting in patients with large resection areas. Given this limitation, the link between specific histopathologic features and GWB remains speculative. Future studies should utilize prospective methods to coregister resective tissue slices to MRI scans, which would allow for colocalization of histopathologic information and MRI signal abnormalities, enabling a stronger inference about the specific tissue characteristics that contribute to abnormal MRI signal.

An additional limitation of the current study is that all patients were taking antiepileptic medications at the time of scanning, whereas all healthy controls were medication-free. Although we attempted to control for the impact of antiepileptic medication use on cognitive test performance by choosing an index that is less sensitive to medications and seizures (Iverson et al. 2006), the impact of antiepileptic medications on GWB is unclear. However, a recent comparison between a sample of 27 patients with Idiopathic Generalized Epilepsy (IGE) and a group of 27 age- and sex-matched healthy control subjects, using the same procedures (i.e., identical scanner, sequence, postprocessing methods, and GWB calculation), revealed no group differences in GWB (McGill 2013). This suggests that an increase in GWB cannot be accounted for by medication use and seizures, but that a histopathologic diagnosis of FCD is an important contributing feature. Notably, unlike FCD, postmortem tissue from patients with IGE does not differ from matched controls on features of microdysgenesis, such as increased IWMN (Opeskin et al. 2000), which is consistent with the speculation that increased IWMNs contribute to GWB.

Conclusion

Results from the current study demonstrate an association between increased GWB and decreased general cognitive abilities. The verification of FCD pathology on resected tissue provides a valuable opportunity to link the presence of dysplasia to both qMRI and cognitive metrics. The majority of the current FCD sample had clinical MRIs interpreted as normal, although GWB was elevated in the resected region. This demonstrates that GWB is a metric that is sensitive to even subtle, visually elusive, dysplastic abnormalities. The presence of a relationship between GWB and cognitive performance in both the healthy control and FCD groups suggests that there are individual differences in tissue features at the cortical gray–white interface that vary on a normal-to-pathologic continuum. Overall, results provide support for the use of GWB as a probe to investigate cognitive and behavioral symptoms in neurologic disease populations, where abnormalities of cortical development are suspected.

Notes

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