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Cortical gray–white matter blurring and declarative memory impairment in MRI-negative temporal lobe epilepsy

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ABSTRACT

Magnetic resonance imaging (MRI)-negative temporal lobe epilepsy (TLE) may be a distinct syndrome from TLE with mesial temporal sclerosis (TLE-MTS). Imaging and neuropsychological features of TLE-MTS are well-known; yet, these features are only beginning to be described in MRI-negative TLE. This study examined whether a quantitative measure of cortical gray and white matter blurring (GWB) was elevated in the temporal lobes ipsilateral to the seizure onset zone of individuals with MRI-negative TLE relative to TLE-MTS and healthy controls (HCs) and whether GWB elevations were associated with neuropsychological comorbidity. Gray–white matter blurring from 34 cortical regions and hippocampal volumes were quantified and compared across 28 people with MRI-negative TLE, 15 people with TLE-MTS, and 51 HCs. Declarative memory was assessed with standard neuropsychological tests and the intracarotid amobarbital procedure (IAP). In the group with MRI-negative TLE (left and right onsets combined), hippocampal volumes were within normal range but GWB was elevated, relative to HCs, across several mesial and lateral temporal lobe regions ipsilateral to the seizure onset zone. Gray–white matter blurring did not differ between the groups with TLE-MTS and HC or between the groups with TLE-MTS and MRI-negative TLE. The group with MRI-negative TLE could not be distinguished from the group with TLE-MTS on any of the standard neuropsychological tests; however, ipsilateral hippocampal volumes and IAP memory scores were lower in the group with TLE-MTS than in the group with MRI-negative TLE. The group with left MRI-negative TLE had lower general cognitive abilities and verbal fluency relative to the HC group, which adds to the characterization of neuropsychological comorbidities in left MRI-negative TLE. In addition, ipsilateral IAP memory performance was reduced relative to contralateral memory performance in MRI-negative TLE, indicating some degree of ipsilateral memory dysfunction. There was no relationship between hippocampal volume and IAP memory scores in MRI-negative TLE; however, decreased ipsilateral IAP memory scores were correlated with elevated GWB in the ipsilateral superior temporal sulcus of people with left MRI-negative TLE. In sum, GWB elevations in the ipsilateral temporal lobe of people with MRI-negative TLE suggest that GWB may serve as a marker for reduced structural integrity in regions in or near the seizure onset zone. Although mesial temporal abnormalities might be the major driver of memory dysfunction in TLE-MTS, a loss of structural integrity in lateral temporal lobe regions may contribute to IAP memory dysfunction in MRI-negative TLE.

1. Introduction

Temporal lobe epilepsy (TLE) is the most common form of drug-resistant focal epilepsy encountered in epilepsy surgery programs [1] and is frequently accompanied by neuropsychological comorbidities [2]. It is an umbrella term that encompasses distinct focal epilepsy syndromes, all of which share electroclinical evidence for seizure onset in

Abbreviations: DNET, dysembryoplastic neuroepithelial tumors; EEG, electroencephalography; FCD, focal cortical dysplasia; HC, healthy control; IAP, intracarotid amobarbital procedure; ICEEG, intracranial electroencephalography; GWB, gray–white matter blurring; MTS, mesial temporal sclerosis; MRI, magnetic resonance imaging; RNS, responsive neurostimulation; TLE, temporal lobe epilepsy.

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the temporal lobe but vary in terms of electrophysiological, neuroimaging, magnetic resonance imaging (MRI), and neuropsychological features [3]. The most common drug-resistant TLE syndrome is TLE with mesial temporal sclerosis (TLE-MTS), which can be diagnosed presurgically by MRI findings of hippocampal atrophy and mesial temporal signal abnormalities, electroencephalographic (EEG) indicators of seizure onset in the mesial temporal lobe, and marked memory morbidity [4]. However, approximately 30% of drug-resistant TLE cases are MRI-negative [3]. In MRI-negative TLE, seizures can originate from various regions of the mesial and/or lateral temporal lobe, and memory functions are variable [5]. The difficulty in localizing the epileptogenic zone has historically led to a reluctance to surgically treat MRI-negative epilepsies. However, the landscape of epilepsy surgery programs is changing. There has been a decrease in surgeries to treat TLE-MTS since 1991, along with an increase in surgeries to treat MRI-negative epilepsies [6]. This calls for a greater understanding of MRI-negative TLE, which may benefit from a different diagnostic and treatment algorithm than TLE-MTS.

Distinguishing TLE-MTS from MRI-negative TLE is important for presurgical decision-making, given higher rates of postsurgical seizure freedom in TLE-MTS [7]. Clinical features that differentiate MRI-negative TLE from TLE-MTS are a later age at seizure onset [8,9] and a higher frequency of seizures with secondary generalization [9,10]. Factors that contribute to poorer seizure outcomes in MRI-negative TLE are a more widespread epileptogenic network, more frequent secondary generalization, and higher preoperative seizure frequency [3,11]. A more widespread epileptogenic network may require larger resection; however, the benefits of a larger resection extent on seizure outcomes in MRI-negative TLE must be weighed against the risk of cognitive decline. The greater the presurgical integrity of the hippocampus and memory functions, the greater the risk of postsurgical memory decline [12,13]. A structurally and functionally intact hippocampus might be spared in surgical approaches to MRI-negative TLE if there is no evidence of hippocampal involvement; thus, potentially sparing memory function. Beyond more tailored approaches to surgical resection, responsive neurostimulation (RNS®, Neuropace) represents another hippocampal-sparing seizure therapy.

One method for presurgically simulating the effects of an anteromesial temporal lobe resection on memory is the intracarotid amobarbital procedure (IAP), which was developed to assess language lateralization [14] and extended to assess memory functions [15]. Low IAP memory scores are generally considered indicators of a loss in hippocampal integrity [16]. However, it is unclear whether extramesial temporal lobe pathology could also lead to reduced IAP memory scores in MRI-negative TLE. The current study aimed to investigate this possibility.

Magnetic resonance imaging-negative TLE is defined by the absence of a lesion on radiological inspection of the MRI [3]. Diagnostic accuracy improves when images are acquired using a high magnetic field epilepsy protocol and interpreted by board-certified radiologists with expertise in the detection of epileptogenic lesions [3], as was the case in the current study. However, the absence of an MRI-visible lesion does not mean the absence of epileptogenic structural pathology, even when an epilepsy imaging protocol is utilized. Postsurgical histological evaluation of resected tissue shows a range of epileptogenic pathologies in MRI-negative TLE such as focal cortical dysplasia (FCD), dysembryoplastic neuroepithelial tumors (DNET), and small temporal pole encephaloceles [17–19], all of which may be too subtle to detect on presurgical radiological evaluation. Advancements in quantitative imaging methods are improving detection of subtle neuropathology, permitting correlation between abnormal morphology and neuropsychological functions. For example, cortical gray and white matter blurring (GWB), which is the hallmark imaging feature of FCD, is associated with lower general cognitive abilities in patients with histopathologically confirmed FCD [20]. In the current study, we aimed to determine whether temporal lobe GWB abnormalities distinguish MRI-negative TLE from TLE-MTS and healthy controls (HCs) and whether extramesial temporal lobe GWB abnormalities in people with MRI-negative TLE are associated with declarative memory impairment.

2. Methods

2.1. Participants

This study was approved by the Internal Review Board at New York University (NYU) School of Medicine. Informed consent was obtained from all participants. Participants with drug-resistant TLE were selected by retrospective review of a consecutive series of patients evaluated for epilepsy surgery at the NYU Comprehensive Epilepsy Center from 2009 to 2017. Patients were included if they (1) had a diagnosis of unilateral focal onset TLE based on clinical history, neurologic evaluation, clinical MRI, continuous video-EEG monitoring, and intracranial electroencephalography (ICEEG) monitoring when available, (2) were between 18 and 65 years of age, (3) had valid results from comprehensive presurgical neuropsychological evaluation, and (4) had a high-resolution T1-weighted scan that passed quality control review. Patients were excluded if they had (1) an MRI-visible lesion in addition to MTS (e.g., low-grade tumors, vascular lesions, hemorrhagic stroke, or encephalopathy) or (2) extratemporal/multifocal seizure onset. Patients with TLE were classified as TLE-MTS by presurgical radiological evaluation and histological confirmation from resected tissue when available. Patients were classified as MRI-negative TLE if presurgical imaging findings from MRIs acquired using a 3-T scanner and epilepsy protocol were interpreted as negative for MTS or any other MRI-visible lesions by board-certified radiologists.

A total of 233 patients signed consent for a research MRI during the recruitment period. Review of clinical records from these patients revealed that 125 met criteria for unilateral TLE. Of these, 35 had an MRI interpreted as normal on radiological evaluation (MRI-negative TLE) and 25 had MTS and no other lesions (TLE-MTS). Twenty-eight patients with MRI-negative TLE and 15 patients with TLE-MTS had a comprehensive presurgical neuropsychological evaluation that included standard neuropsychological tests and the IAP.

Healthy controls were recruited from the community and included if they (1) were between 18 and 65 years of age and (2) had no history of self-reported neurologic or psychiatric disease. Healthy controls were excluded if they had incidental findings on research MRI scans or did not pass scan quality control review.

2.2. Clinical data

Clinical data abstracted from medical records included age at seizure onset, duration of epilepsy, side of seizure onset (left, right), and handedness.

2.3. Neuropsychological test data

Neuropsychological testing was completed as part of the standard presurgical assessment in patients and as part of the research protocol in HCs. General cognitive abilities in patients and HCs were assessed with the General Abilities Index (GAI), an optional index derived from the Wechsler Adult Intelligence Scale [21,22]. The GAI provides an estimate of general cognitive ability with reduced emphasis on working memory and processing speed relative to the Full-Scale intelligence quotient (IQ) score, making it less sensitive to clinically fluctuating factors such as mood, medications, and recent seizures [23,24]. General Abilities Index scores were compared across the groups with MRI-negative TLE, TLE-MTS, and HC.

Declarative memory was assessed in patients with the Logical Memory and Visual Reproduction subtests from the Wechsler Memory Scale (WMS) [25,26]. The Rey Complex Figure Test was administered to patients and HCs as a measure of visual memory [27]. List learning tests were used to assess verbal learning and recall in both patients and

HCs; however, test versions varied for clinical reasons in patients and thus, were not analyzed. In both patients and HCs, visual confrontation naming was assessed with the Boston Naming Test total correct score [27], and verbal fluency was assessed with the Controlled Oral Word Association Test and Animal Naming [27,28]. Executive functioning was assessed with the Trail Making Test Part B and Wisconsin Card Sorting Test-64 Version perseverative errors score [27,28]. Raw scores on these language and executive functioning measures were acquired from patients and HCs and compared across the groups with MRI-negative TLE, TLE-MTS, and HC.

2.4. Intracarotid amobarbital procedure (IAP) data

The IAP was completed as part of the standard presurgical assessment in patients and was not collected in HCs. The IAP procedures used at our center have previously been detailed [29]. An interventional neuroradiologist injected sodium amobarbital into one hemisphere at a time through a catheter placed within the internal carotid artery, above the bifurcation point, guided by roadmap and digital subtraction angiography (DSA) at two frames per second during manual injection of 50–80% concentration of nonionic contrast. The second injection was performed at least 30 min after the initial injection. The hemisphere ipsilateral to the presumed seizure onset zone was injected first to test the integrity of language and memory functions in the contralateral hemisphere. The second injection was performed on the hemisphere contralateral to the presumed seizure onset zone at least 30 min after the initial injection. Adequate hemispheric injection was determined by neurologic examination (contralateral hemiplegia, facial weakness, or dysarthria with or without aphasia). Doses were titrated to each individual to ensure sufficient effect. The patient's level of participation in the procedure was continually assessed through verbal and nonverbal modalities throughout the procedure.

Language was assessed with three phrase repetitions, five auditory commands, and naming of eight objects and four pictures (black and white line drawings). The patient was asked to name aloud each stimulus as it was visually presented. If the patient was able to correctly name the object, they were then asked to remember the object. If the patient was unable to name or incorrectly named the object, they were given the correct name and then told to remember the object (i.e., “This is a hairbrush; remember the hairbrush”). Language lateralization was determined by disruption (complete or partial) of language during the injection. Language was considered bilateral if there was complete or partial disruption of language with both injections or if only incomplete disruption of language was observed with one injection.

Immediately after stimulus presentation, language and motor functions were reassessed to ascertain residual hemispheric anesthesia. In all cases, at the end of stimulus presentation, there was continued evidence of drug effect. Ten minutes after injection or after the patient returned to baseline (whichever was longer), the patient was asked to spontaneously recall any objects or pictures that were shown. Next, the patient was presented with target items and foils and asked to indicate whether they had viewed the item previously (yes/no). We computed a discrimination score in order to account for hits and false positives: [Hits − (False Positives ∗ 0.5)]. One false positive per injection was allowed without penalty to the score. These Wada memory scores, which ranged from 0 to 12, were obtained in patients only and compared between the groups with MRI-negative TLE and TLE-MTS. “Ipsilateral” memory scores refer to scores obtained from the hemisphere ipsilateral to the presumed seizure onset zone (i.e., when the hemisphere opposite to the presumed seizure onset zone was anesthetized), and “contralateral” memory scores refer to scores obtained when the hemisphere containing the presumed seizure onset zone was anesthetized.

2.5. Neuroimaging data: quantitative MRI metrics

Magnetic resonance imaging data were collected using a 3-Tesla Siemens Allegra head-only dedicated research scanner. The acquired images included a 3-plane localizer and a T1-weighted volume pulse sequence (TE = 3.25 ms, TR = 2530 ms, TI = 1100 ms, flip angle = 7° field of view (FOV) = 256 mm, matrix = 256 × 256, voxel size = 1 × 1 × 1.3 mm, scan time: 8:07 min). Image acquisition parameters were optimized to increase gray and white matter contrast. The T1-weighted image was reoriented into a common space, roughly similar to alignment based on the anterior commissure-posterior commissure (AC-PC) line. The images were further refined and normalized using the FreeSurfer 5.1 software package (http://surfer.nmr.mgh.harvard.edu/).

Standard FreeSurfer MRI postprocessing procedures for image segmentation, tessellation, cortical inflation, parcellation, and labeling were utilized [30–32]. For quality control purposes, visual inspection of hippocampal segmentation and cortical surface segmentation was performed by trained, blinded technicians. If errors were detected, manual corrections were applied and reconstructions repeated until accurate segmentations were obtained. FreeSurfer hippocampal segmentation has been validated against manual tracing of the hippocampus [31,33,34]. In order to control for individual variation in brain size, hippocampal volumes were divided by total supratentorial volume.

Surface reconstruction was performed by classifying all white and gray matter voxels in the MRI volume to identify the gray–white matter boundary. The gray–white matter boundary was delineated up to submillimeter accuracy by further refining the white matter cortical surface. Gray–white matter blurring was estimated by calculating the nonnormalized T1 image intensity contrast ([gray − white] / [gray + white]) at 0.5 mm above vs. below the gray–white interface with trilinear interpolation of the images [20,35]. The 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. Therefore, higher GWB values indicate a greater degree of blurring at the gray–white junction.

A parcellation scheme was used to segment cortical regions based on correspondence between local gyrosulcal curvature information in the individual participant's brain and the labeled atlas brain [32]. For each participant, GWB was averaged across 34 cortical regions [32], and these regional averages were used in subsequent analyses.

All MRI metrics were derived separately for the left and right hemispheres and labeled “ipsilateral” if they were extracted from the same hemisphere as the EEG seizure onset zone and “contralateral” if they were from the opposite hemisphere. In HCs, ipsilateral variables were comprised of 56% left and 44% right hemisphere values (contralateral = 44% right and 56% left) to ensure that these variables were comparably proportioned to the patient groups (24 patients with left-sided seizure onset and 19 patients with right-sided seizure onset).

2.6. Statistical analysis

Statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) Version 23. Demographic data (i.e., age, gender, handedness) were compared across the groups with MRI-neg TLE, TLE-MTS, and HC using analysis of variance for continuous variables and chi-square for categorical variables. Clinical data (i.e., side of onset, age at seizure onset, duration of epilepsy) were compared between the groups with MRI-negative TLE and TLE-MTS to identify any potential confounding variables. Neuropsychological test scores, IAP memory scores, and MRI metrics were compared using analysis of covariance. Pairwise comparisons of ipsilateral and contralateral IAP memory scores were performed in the group with MRI-negative TLE to determine whether there was greater impairment on ipsilateral side to seizure onset. A statistical threshold of $p < 0.05$ was utilized. Bonferroni adjustment was applied to GWB comparisons across 34 cortical regions of interest ($p < 0.0015$). Post hoc t-test results were evaluated to further specify group differences.

Correlations between abnormal GWB elevations and memory scores were performed to determine whether GWB elevations were associated with reduced memory performance. Additional correlations between GWB elevations and neuropsychological test results were performed to determine the discriminant validity of memory findings (i.e., is elevated GWB associated with reduced neuropsychological functions across all domains or just memory?). Given evidence for more pronounced memory deficits in patients with left hemisphere TLE [2,36], neuropsychological test performance and clinical correlations were also performed in the group with left MRI-negative TLE separately (N = 18). Clinical correlations were not performed in the group with right MRI-negative TLE because of sample size limitations (N = 10).

3. Results

3.1. Participants

Fifty-one HCs, 28 patients with MRI-negative TLE, and 15 patients with TLE-MTS met criteria for inclusion in this study. There were no differences in age, gender distribution, or handedness distribution between the three groups (Table 1). There were no differences between the groups with MRI-negative TLE and TLE-MTS in the side of seizure onset, age at seizure onset, or duration of epilepsy (see Table 1).

3.2. IAP scores

Group findings from IAP language and memory performance are detailed in Table 1. All patients showed left hemisphere dominance for language in the group with TLE-MTS; however, there were five patients with bilateral language representation in the group with MRI-negative TLE, four of whom had a presumed seizure focus in the left hemisphere. Ipsilateral IAP memory scores ranged from 1 to 12 in the group with MRI-negative TLE and 0 to 12 in the group with TLE-MTS. Contralateral IAP memory scores ranged from 5 to 12 in the group with MRI-negative TLE and from 2 to 12 in the group with TLE-MTS. The group with TLE-MTS had lower ipsilateral IAP memory scores than the group with MRI-negative TLE (Table 1). There were no group differences in contralateral IAP memory scores. Pairwise comparisons showed that ipsilateral memory scores were lower than contralateral memory scores in the group with MRI-negative TLE ($t = -2.18$; $p = 0.04$) and the group with TLE-MTS ($t = -2.81$; $p = 0.01$).

3.3. Neuropsychological test scores

Results from neuropsychological testing in the groups with TLE compared with HCs are detailed in Table 1 and for the groups with left hemisphere onset TLE in Table 2. There were no differences between the groups with MRI-negative TLE, TLE-MTS, and HC in GAI scores; however, when the left-onset groups were compared with HCs, both the groups with MRI-negative TLE (mean = 92) and TLE-MTS (mean = 90) had lower scores than the HCs (mean = 109).

Wechsler Memory Scale memory scores did not differ between the groups with MRI-negative TLE and TLE-MTS, even when the left-onset groups were examined separately. In addition, there were no group differences between MRI-negative TLE, TLE-MTS, and HCs in visual memory on the Rey Complex Figure Delayed Recall Test.

On language tests, no group differences were apparent in Visual Confrontation Naming or Animal Naming; however, groups differed in phonemic fluency on the FAS Test, with post hoc t-tests showing lower scores in the group with MRI-negative TLE relative to HCs ($p = 0.049$). This difference was more pronounced when the group with left-onset MRI-negative TLE was compared with HCs ($t = 5.1$; $p = 0.03$). However, the group with left-onset MRI-negative TLE could not be distinguished from the group with left-onset TLE-MTS on any of the language tests.

There were no group differences on executive functioning measures, including when patients with left-onset were examined separately.

In sum, patients with MRI-negative TLE could not be distinguished from patients with TLE-MTS on standard presurgical neuropsychological tests, even when patients with left-onset TLE were examined separately. However, when patients with left-onset MRI-negative TLE were compared with HCs, deficits in general cognitive abilities and verbal fluency were observed.

3.4. Hippocampal volumes

Hippocampal volumes (adjusted for total supratentorial volume) from the hemisphere ipsilateral to seizure onset differed across the groups with MRI-negative TLE, TLE-MTS, and HC (Table 3). Post hoc t-tests revealed that ipsilateral hippocampal volumes were lower in TLE-MTS than in MRI-negative TLE ($p < 0.001$) and HCs ($p < 0.001$), but there was no difference between MRI-negative TLE and HCs ($p = 0.48$). There were no group differences in contralateral hippocampal volumes. This indicates that reduced hippocampal volumes were

Table 1
Demographic, clinical, and neuropsychological group comparisons.

	MRI-neg TLE (N = 28)	TLE-MTS (N = 15)	HC (N = 51)	Chi-square	p-value
Gender (males/females)	11/17	5/10	26/25	1.9	0.38
Handedness (L/R)	3/25	2/13	3/48	1.7	0.79
Side of onset (L/R)	18/10	6/9		2.3	0.13
	Mean (SD)	Mean (SD)	Mean (SD)	F-value	p-value
Age	37.4 (11.4)	34.1 (9.1)	34.0 (11.6)	0.9	0.42
Epilepsy duration	18.4 (13.3)	20.3 (15.1)		0.2	0.68
Age at seizure onset	18.7 (12.2)	15.1 (8.1)		1.1	0.30
Ipsilateral IAP memory	8.1 (3.2)	5.4 (3.4)		5.7*	0.02*
Contralateral IAP memory	9.8 (2.4)	8.9 (3.6)		0.7	0.41
WAIS-General Abilities Index	101.33 (16.9)	98.67 (19.9)	108.8 (16.1)	2.9	0.06
WMS-Logical Memory II	8.3 (4.3)	8.6 (3.3)		0.1	0.82
WMS-Visual Reproduction II	9.6 (3.7)	7.9 (2.9)		2.1	0.16
Rey Complex Figure Delay	11.7 (7.3)	13.1 (7.0)	13.9 (8.5)	0.6	0.56
Boston Naming Test	49.7 (10.7)	49.7 (8.0)	53.4 (4.8)	2.7	0.07
FAS Test	36.2 (13.8)	35.5 (19.3)	44.8 (9.0)	3.7	0.03
Animal Naming Test	19.2 (6.7)	16.7 (5.2)	20.6 (4.9)	2.1	0.13
Trailmaking Test B	82.8 (40.1)	80.2 (33.9)	70.1 (38.7)	1.1	0.34
WCST Perseverative Errors	9.6 (5.9)	11.3 (7.1)	9.9 (9.0)	0.2	0.82

TLE = temporal lobe epilepsy; MTS = mesial temporal sclerosis; HC = healthy control; L = left; R = right; B = bilateral; SD = standard deviation; WAIS = Wechsler Adult Intelligence Scale III or IV; WMS = Wechsler Memory Scale III or IV; WCST = Wisconsin Card Sorting Test.
* Significant at $p < 0.05$.

Table 2
Demographic, clinical, and neuropsychological group comparisons (left onset).

	L MRI-neg TLE (N = 18)	L TLE-MTS (N = 6)	HC (N = 51)	Chi-square	p-value
Gender (males/females)	8/10	0/6	26/25	5.6	0.06
Handedness (L/R)	3/15	0/6	3/47	3.1	0.54
	Mean (SD)	Mean (SD)	Mean (SD)	F-value	p-value
Age	39.7 (10.7)	36.3 (8.2)	34.0 (11.6)	1.7	0.86
Epilepsy duration	20.3 (14.2)	22.7 (16.1)		0.1	0.74
Age at seizure onset	18.6 (12.7)	14.7 (9.8)		0.5	0.50
Ipsilateral IAP memory	8.9 (2.6)	6.2 (4.3)		3.2	0.09
Contralateral IAP memory	9.3 (2.3)	7.4 (3.0)		2.2	0.15
WAIS-General Abilities Index	91.6 (37.6)	90.2 (12.5)	108.8 (16.1)	4.8	0.01*
WMS-Logical Memory II	8.7 (4.9)	8.0 (1.8)		0.1	0.79
WMS-Visual Reproduction II	10.3 (3.9)	9.0 (2.9)		0.4	0.56
Rey Complex Figure Delay	12.8 (7.9)	15.4 (5.7)	13.9 (8.5)	0.2	0.84
Boston Naming Test	50.9 (9.3)	47.7 (9.0)	53.4 (4.8)	2.8	0.07
FAS Test	35.1 (14.6)	36.2 (20.5)	44.8 (9.0)	3.6	0.04*
Animal Naming Test	17.7 (8.4)	17.0 (3.5)	20.6 (4.9)	1.4	0.25
Trailmaking Test B	72.6 (50.6)	77.7 (20.0)	70.1 (38.7)	0.1	0.94
WCST Perseverative Errors	8.4 (5.4)	14.8 (9.9)	9.9 (9.0)	0.9	0.41

L = left; TLE = temporal lobe epilepsy; MTS = mesial temporal sclerosis; HC = healthy control; L = left; R = right; B = bilateral; SD = standard deviation; WAIS = Wechsler Adult Intelligence Scale III or IV; WMS = Wechsler Memory Scale III or IV; WCST = Wisconsin Card Sorting Test.
* Significant at $p < 0.05$.

specific to the ipsilateral hemisphere in people with TLE-MTS, consistent with the diagnostic criteria for MTS, and that hippocampal volumes were within normal range in the group with MRI-negative TLE.

3.5. Gray–white blurring abnormalities

After correction for multiple comparisons, group differences in GWB were observed in the ipsilateral superior temporal region, the bank of the superior temporal sulcus, the parahippocampal region, and the temporal pole, as well as the contralateral bank of the superior temporal sulcus (Table 3). In all of these regions, post hoc t-test analyses revealed more blurring in the group with MRI-negative TLE, relative to HCs (Fig. 1; ipsilateral superior temporal: $p = 0.0002$; ipsilateral bank of the superior temporal sulcus: $p = 0.0004$; ipsilateral parahippocampal: $p = 0.001$; ipsilateral temporal pole: $p = 0.0001$; ipsilateral entorhinal: $p = 0.002$; contralateral bank of the superior temporal sulcus: $p = 0.0004$); however, there were no differences in GWB between the groups with MRI-negative TLE and TLE-MTS or between the groups with TLE-MTS and HC. Taken together, these results suggest abnormally elevated GWB in people with MRI-negative TLE that is specific to the temporal lobe and more widespread in the temporal lobe ipsilateral to seizure onset, spanning mesial and lateral temporal regions.

3.6. Clinical correlates of GWB abnormalities in left hemisphere MRI-negative TLE

Ipsilateral IAP memory scores were not associated with ipsilateral hippocampal volumes in the group with left hemisphere MRI-negative TLE ($r = -0.11$; $p = 0.70$); however, they were inversely correlated with GWB in the left superior temporal region ($r = -0.61$; $p = 0.013$), indicating that the greater the degree of blurring, the lower the left IAP memory score (see Fig. 2). There were no other neuropsychological correlates of temporal lobe GWB abnormalities.

4. Discussion

Our study shows a higher degree of temporal lobe GWB in patients with MRI-negative TLE relative to HCs, as well as a relationship between GWB elevations in the left superior temporal lobe and lower IAP memory performance. This calls into question a direct link between IAP memory impairment and hippocampal abnormalities in patients with MRI-negative TLE, indicating that in patients with seizure onset in the left temporal lobe, low IAP scores might be obtained in the context of a volumetrically normal hippocampus. This information, when combined with information obtained from ICEEG, could improve algorithms for presurgical decision-making in drug-resistant TLE. For example, if there is no evidence for epileptogenicity in the hippocampus of a patient with left lateral temporal lobe seizure onset and GWB abnormalities, then low IAP scores should not necessarily or solely be considered an indicator of hippocampal pathology. They could also potentially reflect structural pathology in the left lateral temporal lobe region.

We also found that the group with MRI-negative TLE could not be distinguished from the group with TLE-MTS by neuropsychological test scores alone. This is consistent with findings from a prior study that investigated imaging markers of memory impairment in MRI-negative TLE and TLE-MTS [5]. They also found no difference in neuropsychological tests of declarative memory; however, lower auditory delayed recall scores were associated with decreased cornu ammonis 1 volume in TLE-MTS but not in MRI-negative TLE. In contrast, lower auditory delayed recall scores were associated with thinning of the fusiform gyrus in MRI-negative TLE [5]. Although the neocortical correlate of declarative memory impairment they identified in the group with MRI-negative TLE did not spatially correspond with our superior temporal finding, this could be due to their reliance on cortical thickness as an imaging marker. Cortical thickness and GWB are both considered MRI markers for FCD, although they may be sensitive to different neuropathological features [37]. Thus, our study findings do not contradict these prior findings but further corroborate neocortical pathology as a marker of declarative memory impairment in MRI-negative TLE and spatially extend the relevant zone to include the superior temporal region.

An additional difference is that we utilized the IAP as a measure of memory performance. The IAP is sensitive to lateralized pathology given that each hemisphere's functional integrity is tested independent from the contributions of the opposite hemisphere. However, it is possible that mesial temporal regions were not completely anesthetized during the IAP procedure, given that only a minority of patients show perfusion of this region [38–40]. This makes it difficult to infer intact mesial temporal lobe function in the context of normal scores as it is possible that the opposite mesial temporal region may be extending functional support. However, interpretation of a relationship between impaired scores and lateral temporal lobe pathology is less problematic because in all cases, lateral temporal regions and the temporal pole are completely anesthetized [39].

The question then becomes why lateral temporal lobe pathology might interfere with memory function during the IAP. It is well established that mesial temporal regions play a critical role in episodic

Table 3
Group comparisons of MRI metrics.

	MRI-neg TLE (N = 28)	TLE-MTS (N = 15)	HC (N = 51)		
	Mean (SD)	Mean (SD)	Mean (SD)	*F*-value	p-value
Brain region					
Supratentorial vol (mm^3)	1,009,503.5 (86,195.2)	993,550.9 (115,473.7)	1,059,030.7 (158,555.0)	1.7	0.20
Ipsi hippo vol (mm^3)	3953.3 (691.5)	3036.4 (762.7)	3793.6 (434.6)	14.2	7E−06**
Contra hippo vol (mm^3)	3897.0 (596.5)	3714.6 (488.2)	3849.6 (418.9)	1.5	0.24
GWB from cortical regions ipsilateral to presumed seizure onset zone					
Temporal pole	−0.115 (0.009)	−0.121 (0.011)	−0.125 (0.011)	9.6*	0.0002**
Entorhinal	−0.114 (0.013)	−0.118 (0.015)	−0.126 (0.135)	6.9	0.002*
Parahippocampal	−0.134 (0.014)	−0.139 (0.014)	−0.146 (0.013)	7.6*	0.001**
Fusiform	−0.126 (0.010)	−0.130 (0.010)	−0.132 (0.009)	4.1	0.02*
Superior temporal	−0.118 (0.010)	−0.124 (0.008)	−0.126 (0.007)	8.8*	0.0003*
Bank of STS	−0.127 (0.009)	−0.133 (0.010)	−0.136 (0.009)	7.8*	0.001**
Inferior temporal	−0.132 (0.011)	−0.134 (0.010)	−0.138 (0.010)	4.1	0.02*
Middle temporal	−0.128 (0.011)	−0.133 (0.010)	−0.135 (0.009)	5.3	0.007*
Frontal pole	−0.120 (0.015)	−0.123 (0.012)	−0.127 (0.013)	1.9	0.15
Superior frontal	−0.121 (0.012)	−0.126 (0.011)	−0.124 (0.009)	1.5	0.22
Rostral middle frontal	−0.129 (0.011)	−0.134 (0.011)	−0.134 (0.010)	2.0	0.143
Caudal middle frontal	−0.116 (0.009)	−0.122 (0.012)	−0.120 (0.020)	1.6	0.203
Pars opercularis	−0.121 (0.010)	−0.126 (0.009)	−0.126 (0.009)	2.8	0.06
Pars triangularis	−0.122 (0.020)	−0.129 (0.011)	−0.128 (0.010)	3.9	0.02*
Pars orbitalis	−0.121 (0.009)	−0.126 (0.011)	−0.126 (0.010)	2.0	0.14
Medial OFC	−0.126 (0.013)	−0.132 (0.013)	−0.132 (0.013)	2.1	0.12
Lateral OFC	−0.124 (0.010)	−0.131 (0.010)	−0.130 (0.010)	3.2	0.05
Precentral	−0.097 (0.008)	−0.102 (0.011)	−0.099 (0.008)	1.7	0.19
Paracentral	−0.097 (0.007)	−0.102 (0.009)	−0.100 (0.008)	2.0	0.14
Postcentral	−0.115 (0.008)	−0.121 (0.009)	−0.118 (0.008)	2.7	0.07
Supramarginal	−0.120 (0.008)	−0.124 (0.010)	−0.126 (0.007)	4.8	0.01*
Superior parietal	−0.118 (0.008)	−0.123 (0.010)	−0.122 (0.007)	4.1	0.02*
Inferior parietal	−0.120 (0.009)	−0.125 (0.008)	−0.125 (0.007)	4.9	0.009*
Precuneus	−0.120 (0.007)	−0.124 (0.009)	−0.125 (0.007)	5.2	0.007*
Lingual	−0.120 (0.007)	−0.125 (0.010)	−0.122 (0.008)	1.6	0.21
Pericalcarine	−0.119 (0.010)	−0.123 (0.012)	−0.119 (0.009)	1.4	0.25
Cuneus	−0.118 (0.008)	−0.121 (0.008)	−0.119 (0.008)	0.5	0.62
Lateral occipital	−0.118 (0.009)	−0.121 (0.008)	−0.120 (0.008)	1.0	0.36
Rostral ACC	−0.126 (0.011)	−0.132 (0.012)	−0.134 (0.011)	4.4	0.02*
Caudal ACC	−0.149 (0.012)	−0.155 (0.012)	−0.154 (0.011)	2.7	0.07
Posterior cingulate	−0.131 (0.010)	−0.134 (0.011)	−0.138 (0.009)	3.7	0.03*
Isthmus cingulate	−0.124 (0.010)	−0.126 (0.012)	−0.128 (0.009)	1.3	0.28
GWB from cortical regions contralateral to presumed seizure onset zone					
Temporal pole	−0.118 (0.013)	−0.127 (0.009)	−0.122 (0.012)	3.1	0.05
Entorhinal	−0.117 (0.013)	−0.123 (0.009)	−0.121 (0.014)	1.3	0.29
Parahippocampal	−0.139 (0.013)	−0.140 (0.009)	−0.145 (0.012)	2.6	0.08
Fusiform	−0.127 (0.010)	−0.132 (0.007)	−0.132 (0.011)	2.8	0.06
Superior temporal	−0.119 (0.009)	−0.125 (0.010)	−0.127 (0.009)	6.4	0.003*
Bank of STS	−0.128 (0.008)	−0.133 (0.011)	−0.137 (0.010)	7.9*	0.001**
Inferior temporal	−0.132 (0.010)	−0.137 (0.009)	−0.137 (0.011)	2.6	0.08
Middle temporal	−0.130 (0.009)	−0.134 (0.009)	−0.145 (0.012)	5.7	0.005*
Frontal pole	−0.122 (0.012)	−0.128 (0.011)	−0.129 (0.012)	3.0	0.06
Superior frontal	−0.121 (0.010)	−0.125 (0.010)	−0.125 (0.011)	1.4	0.26
Rostral middle frontal	−0.130 (0.010)	−0.134 (0.012)	−0.135 (0.010)	1.9	0.16
Caudal middle frontal	−0.117 (0.010)	−0.120 (0.011)	−0.121 (0.011)	1.1	0.33
Pars opercularis	−0.123 (0.010)	−0.126 (0.011)	−0.127 (0.010)	1.5	0.23
Pars triangularis	−0.124 (0.010)	−0.130 (0.011)	−0.129 (0.010)	2.7	0.07
Pars orbitalis	−0.122 (0.009)	−0.125 (0.013)	−0.127 (0.011)	2.1	0.13
Medial OFC	−0.131 (0.010)	−0.132 (0.013)	−0.136 (0.011)	2.1	0.12
Lateral OFC	−0.126 (0.010)	−0.130 (0.011)	−0.131 (0.011)	2.0	0.15
Precentral	−0.098 (0.008)	−0.102 (0.011)	−0.099 (0.008)	1.1	0.32
Paracentral	−0.100 (0.010)	−0.104 (0.009)	−0.101 (0.008)	1.1	0.35
Postcentral	−0.115 (0.008)	−0.122 (0.009)	−0.117 (0.008)	2.6	0.08
Supramarginal	−0.120 (0.009)	−0.124 (0.011)	−0.126 (0.008)	3.7	0.03*
Superior parietal	−0.117 (0.008)	−0.123 (0.010)	−0.121 (0.008)	3.5	0.03*
Inferior parietal	−0.120 (0.009)	−0.123 (0.010)	−0.126 (0.008)	3.9	0.02*
Precuneus	−0.119 (0.008)	−0.124 (0.009)	−0.125 (0.008)	3.7	0.03*
Lingual	−0.119 (0.008)	−0.122 (0.012)	−0.121 (0.008)	0.7	0.50
Pericalcarine	−0.118 (0.008)	−0.125 (0.013)	−0.117 (0.009)	4.5	0.01*
Cuneus	−0.116 (0.008)	−0.123 (0.011)	−0.117 (0.008)	3.3	0.04*
Lateral occipital	−0.117 (0.009)	−0.121 (0.008)	−0.121 (0.008)	1.9	0.16
Rostral ACC	−0.128 (0.012)	−0.131 (0.013)	−0.132 (0.012)	1.0	0.36
Caudal ACC	−0.151 (0.014)	−0.155 (0.017)	−0.157 (0.012)	1.9	0.16
Posterior cingulate	−0.131 (0.011)	−0.135 (0.011)	−0.137 (0.009)	2.7	0.07
Isthmus cingulate	−0.121 (0.013)	−0.123 (0.011)	−0.126 (0.010)	1.9	0.16

memory formation, with recall profoundly reduced by electrophysiological disruption of the hippocampus, amygdala, and parahippocampal gyrus during the encoding or retrieval stage [41]. However, disruption of lateral temporal regions also impairs memory function [42], and intracranial recordings from lateral temporal cortex (inferior, middle, and temporal gyri) show robust activation during encoding of verbal items that are later successfully recalled [43–46]. In one case from a combined IAP and single photon emission computed tomography study [39], a patient showed the absence of any mesial temporal hypoperfusion during the IAP yet still failed the memory procedure. In this case, extramesial temporal pathology could explain such a failure. The left lateral temporal lobe may play a greater role in declarative memory when there is a high verbal demand, as was the case with our IAP memory procedures, whereby patients were asked to name each item during the encoding phase.

Intracranial recording during "subsequent memory" paradigms (i.e., activity during encoding of recalled versus forgotten items) reveals much more robust lateral temporal involvement [47–49] than what is reported in the meta-analyses of functional MRI studies [50,51]. This discrepancy has been attributed to a lack of spatial precision in fMRI studies [52]. Several recent publications have demonstrated that direct electrical stimulation of left lateral temporal regions, but not mesial temporal or prefrontal regions, during encoding of a 12-item word list can boost subsequent word recall [45,46]. These memory boosting effects have proved to be inconsistent in stimulation of mesial temporal regions [53–55]. In addition, in a double-blind, randomized, controlled study of the RNS® system in patients with treatment-resistant focal epilepsy, responsive closed-loop stimulation of neocortical regions resulted in stabilization of verbal memory functions and improvement in naming [56]. Thus, the left lateral temporal region may represent a therapeutic target for direct electrical or noninvasive stimulation for people with left MRI-negative TLE and comorbid memory disorder.

Although this study aimed to identify MRI and neuropsychological features that distinguish MRI-negative TLE from TLE-MTS, many of the direct comparisons between these two groups revealed similar features, which highlight the difficulty in making this clinical distinction presurgically. The only features that distinguished TLE-MTS from MRI-negative TLE were ipsilateral hippocampal volumes and IAP memory scores, both of which were lower in TLE-MTS. However, findings from comparisons between MRI-negative TLE and HCs are noteworthy because they contribute to the emerging clinical characterization of MRI-negative TLE. These findings include reduced general cognitive abilities and verbal fluency in the group with left-onset MRI-negative TLE and elevated GWB in the temporal lobe ipsilateral to the side of seizure onset in the combined left and right-onset groups. These features should continue to be investigated in larger samples of people with MRI-negative TLE.

A total of 21 of our 28 patients with MRI-negative TLE proceeded to anterior temporal lobe resection with histological evaluation of the resected temporal lobe tissue. In all of these cases, there was a report of FCD, with findings that ranged from focal cortical dyslamination, increased interstitial white matter neurons, dysmorphic neurons, to focal decreases in neuronal density, all of which could feasibly contribute to elevated cortical GWB. However, standardized criteria for classifying FCD subtypes were not consistently applied [57]; therefore, FCD subtypes could not be established. Focal regions of mild to moderate neuronal loss were observed in the hippocampus of 10 patients and dysplastic neurons in another 6 patients, suggesting that some degree of hippocampal pathology was also a common feature in the group with MRI-negative TLE. Although not available on all patients, these histological findings suggest that the majority of patients in the MRI-negative TLE sample had focal temporal lobe pathology, albeit too subtle to be apparent on MRI. Developmental anomalies such as FCD could contribute to functional reorganization, as suggested by the presence of patients with bilateral language representation in the group with MRI-negative TLE. In the absence of direct MRI-pathology correspondence, we cannot infer that GWB is a marker of FCD; however, localization of GWB abnormalities to the ipsilateral temporal lobe validates GWB as a measure of general pathologic disruption in MRI-negative TLE.

Limitations of our study include a small sample size of individuals with TLE-MTS, which compromised the evaluation of neural correlates of IAP memory impairment in this group. Therefore, we rely on prior evidence for a relationship between hippocampal volume loss and memory impairment in TLE-MTS to discriminate markers of memory impairment between MRI-negative TLE and TLE-MTS [5]. The relatively smaller sample size of individuals with TLE-MTS may have resulted in decreased power to detect group differences between MRI-negative TLE and TLE-MTS. Evaluation of GWB group comparison results in Table 3 shows a fairly consistent pattern of GWB values in the group with TLE-MTS falling somewhere in between the groups with MRI-negative TLE and HC or closer to the HC group. Although the current study highlights GWB as a feature that distinguishes people with MRI-negative TLE from HCs, future studies with a larger sample size of patients with TLE-MTS should continue to investigate the role of GWB in distinguishing MRI-negative TLE from TLE-MTS. In addition, we did not have a sufficient number of individuals with MRI-negative TLE and right hemisphere seizure onset to determine whether extramesial temporal correlates of IAP memory impairment might also be apparent in this group.

Although we did not find a relationship between GWB abnormalities and memory performance on standard neuropsychological tests, this may be due to several factors. First, some of the memory tests that we used (e.g., Logical Memory) do not have strong lateralizing value in epilepsy but may instead rely on bilateral support [58]. Second, the functional "knock-out" approach used in the IAP might allow for a more sensitive measure of hemispheric functional integrity. Third, sample size reductions when groups are stratified into left and right onset may also play a role; it is possible that additional GWB correlates of memory impairment may become apparent in a larger sample of individuals with left MRI-negative TLE.

An additional limitation is that the antiepileptic drug (AED) burden was high in most patients, although comparable across groups. Ten patients were on carbonic anhydrase inhibitors (eight in the group with MRI-negative TLE and two in the group with TLE-MTS), which may have negatively impacted their cognitive performance. Given the diversity in medication type and dosing profiles, we were unable to model medication effects in our analyses. Thus, it is possible that variance in performance associated with AEDs could have increased noise in cognitive test scores and reduced sensitivity to group differences and correlations with MRI metrics.

It is important to note that decisions about surgical extent are informed by clinical history, intracranial EEG, imaging, and neuropsychological test results, in addition to results from IAP testing. The IAP results are only a small part of a much larger set of clinical information used to guide surgical planning. With that said, our results suggest that low IAP scores do not uniformly and solely indicate mesial temporal lobe pathology in TLE but may also be associated with a loss of structural

Notes to Table 3:
Hippocampal volumes were adjusted for total supratentorial volumes for statistical analyses, but unadjusted values are reported here for ease of interpretation. Gray–white matter blurring (GWB) is a ratio score reflecting white matter (wm) and gray matter (gm) intensity values [(gm − wm) / gm + wm) sampled 0.5 mm from the cortical gray and white matter junction. Values range from −1 to 0 with values closer to 0 indicating more blurring of the gray–white junction.
TLE = temporal lobe epilepsy; MTS = mesial temporal sclerosis; HC = healthy control; SD = standard deviation; STS = superior temporal sulcus; OFC = orbitofrontal cortex; ACC = anterior cingulate cortex.
* Significant at $p < 0.05$.
** Significant at Bonferroni adjusted threshold of $p < 0.0015$.

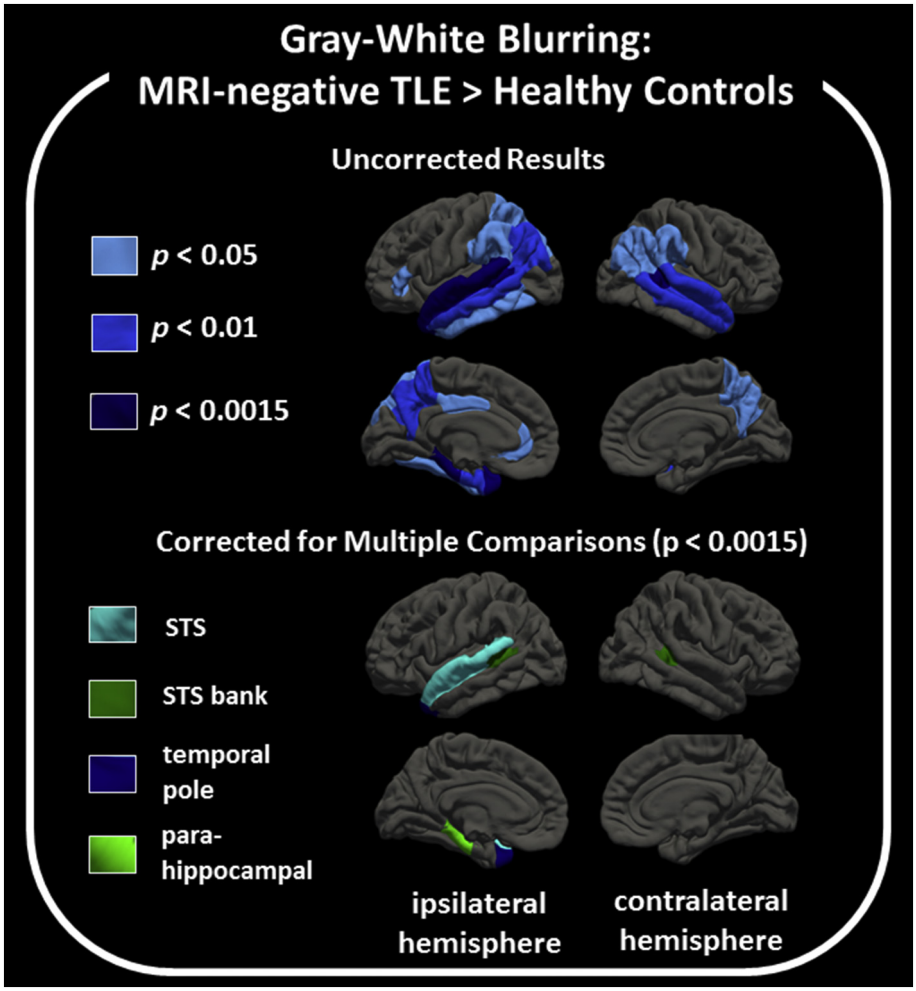

Fig. 1. Cortical gray and white matter blurring (GWB) abnormalities in MRI-negative temporal lobe epilepsy (TLE) relative to healthy controls. Uncorrected results from t-test comparisons revealed GWB elevations in MRI-negative TLE across the ipsilateral temporal lobe, pars triangularis, parietal lobe, cingulate gyrus, and precuneus. Contralateral elevations spanned the middle and superior temporal lobe, inferior parietal lobe, and precuneus. After multiple comparison correction, GWB was elevated in the ipsilateral superior temporal region ($p = 0.0002$); ipsilateral bank of the superior temporal sulcus ($p = 0.0004$); ipsilateral parahippocampal region ($p = 0.001$); ipsilateral temporal pole ($p = 0.0001$); ipsilateral entorhinal region ($p = 0.002$); and the contralateral bank of the superior temporal sulcus ($p = 0.0004$) relative to healthy controls.

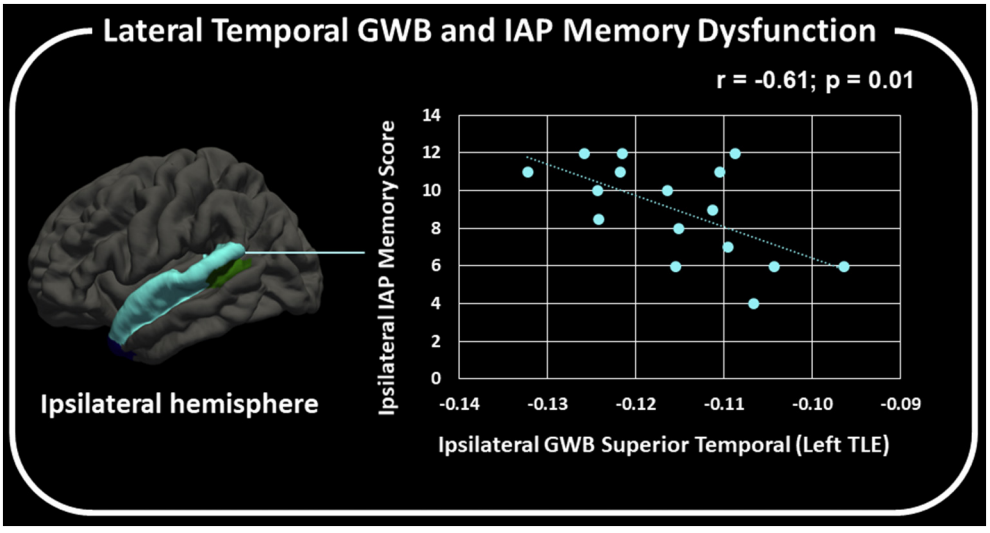

Fig. 2. Cortical gray and white matter blurring (GWB), averaged across the superior temporal lobe, was inversely correlated with intracarotid amobarbital procedure (IAP) memory scores obtained from the ipsilateral hemisphere (i.e., when the contralateral hemisphere was anesthetized) in people with left MRI-negative temporal lobe epilepsy (TLE). Gray and white matter blurring scores range from −1 to 0, with 0 representing the highest degree of blurring. Intracarotid amobarbital procedure memory scores range from 0 to 12 with 12 representing the highest score possible.

integrity in the left lateral temporal lobe. This may be of use in surgical planning; however, corroboration from other sources is needed in each individual case.

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Ethical statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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