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STATISTICAL VOXEL-WISE ANALYSIS OF ICTAL SPECT REVEALS PATTERN OF ABNORMAL PERFUSION IN PATIENTS WITH TEMPORAL LOBE EPILEPSY

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ABSTRACT - *Objective:* To investigate the pattern of perfusion abnormalities in ictal and interictal brain perfusion SPECT images (BSI) from patients with temporal lobe epilepsy (TLE). *Method:* It was acquired interictal and ictal BSI from 24 patients with refractory TLE. BSIs were analyzed by visual inspection and statistical parametric mapping (SPM2). Statistical analysis compared the patients group to a control group of 50 volunteers. The images from patients with left-TLE were left-right flipped. *Results:* It was not observed significant perfusional differences in interictal scans with SPM. Ictal BSI in SPM analysis revealed hyperperfusion within ipsilateral temporal lobe (epileptogenic focus) and also contralateral parieto-occipital region, ipsilateral posterior cingulate gyrus, occipital lobes and ipsilateral basal ganglia. Ictal BSI also showed areas of hypoperfusion. *Conclusion:* In a group analysis of ictal BSI of patients with TLE, voxel-wise analysis detects a network of distant regions of perfusional alteration which may play active role in seizure genesis and propagation.

KEY WORDS: brain perfusion, SPECT, SPM, seizures, epilepsy.

Análise estatística baseada em voxel do SPECT ictal revela um padrão de alteração perfusional em pacientes com epilepsia de lobo temporal

RESUMO - *Objetivo:* Investigar o padrão de anormalidades perfusionais no SPECT de perfusão cerebral (SPC) ictal e interictal na epilepsia de lobo temporal (ELT). *Método:* Foram realizados SPCs ictal e interictal de 24 pacientes com ELT que foram analisados visualmente e com o statistical parametric mapping (SPM2). A análise estatística comparou o grupo de pacientes versus um grupo controle de 50 voluntários. *Resultados:* Na análise do SPM não foram observadas diferenças significativas no grupo de SPC interictal. No grupo de SPC ictal o SPM revelou hiperperfusão no lobo temporal ipsilateral (foco epileptogênico) e também na região parieto-occipital contralateral, porção posterior do cíngulo ipsilateral, lobos occipitais e núcleos da base ipsilateral. O SPC ictal também mostrou áreas de hipoperfusão. *Conclusão:* Em uma análise de grupo do SPC ictal de pacientes com ELT, a análise baseada em voxel detecta uma rede de alteração perfusional em regiões distantes que pode ter uma função ativa na origem e propagação das crises.

PALAVRAS-CHAVE: Perfusão cerebral, SPECT, SPM, crises epilépticas, epilepsia.

Epilepsy affects 0.5 to 1% of the world population[1]. Anti-epileptic drugs successfully control seizures in most patients with epilepsy. Surgical treatment of epilepsy is a therapeutic option for those patients who do not achieve a seizure-free status with medication and have a focal brain lesion accounting for the origin of seizures. Medial temporal lobe epilepsy (TLE) is both the most frequent form of epilepsy as well as the form that accounts for the majority of epilepsy patients submitted to surgery, which is performed by hippocampal removal. Histological analysis of the specimen resect-

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ed reveals hippocampal sclerosis in nearly 60% in patients with medial TLE[2]. The success of the surgery relies on techniques that help identify the source and side of the seizures. Brain perfusion SPECT (single photon emission computed tomography) is an accurate method for detecting the seizure origin.

Two common brain perfusion SPECT radiotracers used for identifying the origin of seizures are ^{99m}Tc-HMPAO (hexamethyl-propyleneamine-oxime) and ^{99m}Tc-ECD (ethyl-cysteinate-dimer). Both are lipophilic amines that are able to cross the blood-brain barrier with extraction rate of approximately 100% after 2 minutes for ^{99m}Tc-HMPAO and 95% after 20 seconds for ^{99m}Tc-ECD. ^{99m}Tc-ECD has the advantage of a higher chemical stability after preparation (6 hours compared to only 30 minutes for ^{99m}Tc-HMPAO). Visual inspection of brain perfusion SPECT images (BSI) is a common method for identifying the epileptogenic focus. Classically, this region appears hypoperfused in the interictal study and becomes hyperperfused in ictal study. The specificity of this combination is nearly 100%. The assessment of interictal BSIs alone has a sensitivity of 44% to detect the source of seizures in patients with TLE, while the sensitivity of the evaluation of the ictal study alone has a sensitivity of up to 96%[3]. In the ictal study, the radiotracer is injected early in a seizure, and BSI is acquired after the seizure has ceased. In these ictal images, the source of the seizure shows stronger uptake of the radiotracer due to its increased metabolic demand and therefore augmented perfusion. In addition to visual inspection, BSI is also suitable for statistical analysis. Statistical analysis of BSI has been used to analyze the regions of the brain that show differences in perfusion in pathologies such as Alzheimer's disease[4], systemic lupus erythematosus[5] and in the evaluation of epileptic foci in BSI[6-8].

In the present study, we conducted a statistical voxel-wise analysis of BSI comparing images from patients with chronic refractory TLE with images from age-matched neurologically healthy controls. Our aim was to identify the pattern of hyperperfusion and hypoperfusion revealed by ictal and interictal BSI. We hypothesized that, as a group, patients with TLE show significant hyperperfusion involving the medial portion of the temporal lobe and its connections.

METHOD

This study complies with the current laws of Brazil and had the previous approval of the Ethics Committee of the School of Medical Sciences, Campinas State University (UNICAMP), Campinas, Brazil.

Patients and control group – Twenty-four patients with chronic drug-refractory TLE were studied (16 women, 8 men; mean age: 26 years). All patients had a clinical diagnosis of TLE as assessed by ictal and interictal EEG. All patients had a structural abnormality in the temporal lobe demonstrated by magnetic resonance imaging (MRI). Lateralization of the epileptogenic focus was based on matching the clinical data, EEG findings and MRI. Histopathological analysis and surgical outcome data were used to confirm the localization of the epileptogenic focus. The control group for the statistical parametric mapping (SPM) consisted of 50 healthy volunteers with ages between 25 and 49 years, mean age 30 years, 29 women and 21 men.

Electroencephalography – All patients underwent serial routine EEG recording using the 10-20 system with additional anterior temporal and zygomatic electrodes. They were also submitted to long-term-video-EEG monitoring with scalp electrodes for seizure recording.

Magnetic resonance imaging (MRI) – MRI was performed in a 2.0 T scanner (Elscint Prestige, Haifa, Israel) using a protocol that consisted of: a) sagital T1 spin-echo, 6 mm thick (TR= 430, TE=12) for optimal orientation of the subsequent images; b) coronal T1 inversion recovery (IR), 3 mm thick (flip angle=200o; TR=2700, TE= 14, TI=840, matrix=130x256, FOV=16x18 cm); c) coronal T2-weighted "fast spin-echo" (FSE), 3-4mm thick (flip angle=120°, TR=4800, TE=129, matrix=252x320, FOV =18x18 cm); d) axial images parallel to the long axis of the hippocampus; T1 gradient echo (GRE), 3mm thick (flip angle=70°, TR= 200, TE= 5, matrix=180x232, FOV =22x22 cm); e) axial T2 FSE, 4mm thick (flip angle=120°, TR=6800, TE=129, matrix=252x328, FOV=21x23 cm); f) volumetric (3D) T1 GRE, acquired in the sagital plane for multiplanar reconstruction, 1 mm thick (flip angle=35°, TR=22, TE=9, matrix=256x220, FOV=23x25 cm).

Visual analysis of MRI and multi-planar reconstruction were systematically performed in a workstation (O2 Silicon Grafic) using the Omnipro software (Elscint Prestige, Haifa, Israel).

Brain perfusion SPECT imaging (BSI) acquisition – Both interictal and ictal studies were acquired for all patients. For all the control participants as well as for the patients' interictal scans, the participants were asked to rest in a dark, quiet room for 15 minutes, with a permanent intravenous access through a butterfly connected to a catheter with saline solution. While at rest, 1110 MBq (30 mCi) of ^{99m}Tc-ECD were injected. The participants rested for another 10 minutes prior to BSI acquisition.

The ictal BSIs were acquired after a spontaneous seizure. Patients were asked to rest while continuous EEG and video were recorded. Patients remained with a permanent intravenous access through a butterfly connected to a catheter with saline solution. To ensure a fast

injection of the radiopharmaceutical the syringe was connected to the catheter and protected with a lead shield. Upon seizure onset, 1110 MBq (30 mCi) of 99mTc-ECD were injected as fast as possible. Seizures were confirmed by EEG and video recordings. BSIs were acquired after the seizure had ended.

BSI was performed in a computed scintillation camera with a fan-beam collimator. Sixty images were acquired in a 64 x 64 matrix, every 6 degrees, in a total of 360 degrees. Raw data were reconstructed by filtered back projection and attenuation correction was performed using Chang's method with a 0.115 attenuation coefficient. Images were displayed in the transaxial, coronal and sagital planes for interpretation. The mean time of the radiotracer injection was 16 seconds (from 4 to 40 seconds).

BSI visual analysis – Qualitative analysis was performed by two experienced nuclear physicians who searched for hypoperfusion or hyperperfusion areas in BSI. This was done through the comparison of the perfusion in cortical and subcortical regions with the perfusion in the cerebellum.

BSI statistical analysis – The reconstructed BSIs were converted into Analyze format using MRIcro software (www.mricro.com). Voxel-based analysis was performed using SPM2 (Wellcome Department of Cognitive Neurology, www.fil.ion.ucl.ac.uk). To allow group comparison, the size and shape of each individual's scans were normalized to stereotaxic space (warping each image to match the default PET template that is distributed with SPM2). This process involves a 12 parameter linear transformation. The normalized images were smoothed by convolution with an Isotropic Gaussian Kernel (FWHM) of 6mm. The ^{99m}Tc-ECD distribution was standardized to the mean global uptake using a proportional scale.

The patients were divided into two groups: right and left epileptogenic focus. The five patients who had bilateral epileptogenic foci were classified as right or left by the video and EEG analysis during the seizure of the ictal BSI. The BSIs from patients with left epileptogenic focus were left-right flipped, in order to render possible to evaluate all MTLE patients in a single group.

Statistical analysis was performed by comparing both the ictal and the interictal studies with the control group. Comparisons between groups were performed using a non-paired two sample t-test. In order to control for familywise errors due to multiple comparisons, we applied a false discovery rate (FDR) statistical threshold of $p < 0.05$ and of $p < 0.01$.

RESULTS

Patient group – Based on the clinical history, EEG and MRI, ten patients were classified as having a right temporal lobe foci, nine as having a left temporal lobe foci and five as having bilateral epileptogenic foci. Three of them (pts. # 3, 12 and 16) had predominance of hippocampal atrophy and signal changes on MRI in one side, ipsilateral to the video-EEG results and ictal brain perfusion SPECT hyperperfusion. The other two patients (pts. # 1 and 22) were classified as right or left by the video-EEG recording at the time of injection for ictal BSI.

Among the 24 patients studied, 19 were submitted to surgery. Histopathological analysis showed medial temporal sclerosis in 10 patients, subpial gliosis in 2 patients, a glial nodule in 1 patient and a ganglioglioma in 1 patient. In 5 patients, the sample was not sufficient for proper histopathological evaluation. The mean follow-up period after surgery was 40 months (3 months to 6 years). Fourteen patients (74%) were classified as Engel class I, four patients (21%) as Engel class II and one (5%) as Engel class III[9].

Two patients were submitted to two surgeries (pts. # 2 and 9) (Table 1). One patient (pt. # 9) persisted with seizures after the first surgery and was submitted to another surgery to widen the margins of the resection. This patient was classified as Engel class II after the second surgery. One patient (pt. # 2) had a ganglioglioma and began with seizures three years after surgery due to incomplete resection of the tumor. This patient was operated on again, being re-classified as Engel class IB. Three patients (pts. # 3, 12 and 16) that were classified as having bilateral epileptogenic foci were operated on because they had predominance of EEG and MRI findings on one side. After surgery one patient (pt. # 3) became seizure free (Engel class I), one patient remained with rare seizures (Engel class IIA) (pt. # 16) and one patient remained in Engel class III (pt. # 12).

Five patients are still waiting for surgery (pts. # 1, 5, 11, 19 and 22). They all showed concordant seizure onset lateralization by MRI, video EEG and ictal BSI.

Visual analysis of brain perfusion SPECT imaging (BSI) – Table 2 displays the findings of the visual analysis of ictal BSI. All patients had hyperperfusion in the epileptogenic focus as determined by clinical-EEG investigation and surgery. Hyperperfusion was also detected in the ipsilateral basal ganglia in thirteen patients and in two patients bilateral basal ganglia hyperperfusion was also noted. Other areas of hyperperfusion were observed on visual analysis: ipsilateral (2/24), contralateral (1/24) and bilateral thalami (2/24); contralateral (1/24) and ipsilateral cerebellar hemisphere (1/24) and contralateral temporal lobe (1/24).

Table 1. Patient data.

Patient	Age (years)	Sex	Side	Histopathology	MRI	Visual analysis (epilept. focus)
1	13	F	B	-	MTS	R
2	2	F	L	GG	CL	L
3	45	F	B (+L)	MTS	MTS	L
4	42	F	L	MTS	MTS	L
5	19	M	L	-	nl	L
6	36	F	R	MTS	MTS	R
7	17	F	R	MTS	MTS	R
8	33	F	R	SPG	MTS	R
9	28	M	L	IM	nl	L
10	31	F	R	MTS	MTS	R
11	9	M	L	-	MTS	L
12	45	M	B (+R)	SPG	MTS	R
13	6	F	R	MTS	MTS	R
14	41	F	R	IM	MTS	R
15	26	M	R	MTS	MTS	R
16	43	F	B (+L)	IM	MTS	L
17	41	F	R	MTS	MTS	R
18	32	F	L	GN	MTS	L
19	21	M	L	-	MTS	L
20	10	M	R	IM	TD	R
21	20	M	L	MTS	MTS	L
22	32	F	B	-	MTS	L
23	17	F	R	IM	MTS	R
24	16	F	L	MTS	MTS	L

F, female; M, male; B, bilateral; L, left; R, right; MTS, medial temporal sclerosis; SPG, subpial gliosis; CL, cystic lesion; IM, insufficient material; TD, temporal dysplasia; GG, ganglioglioma; nl, normal; GN, glial nodule; +L or +R, more intense at left or right side.

Table 2. Visual analysis of ictal brain perfusion SPECT: areas of hyperperfusion.

Areas	Number of patients
Temporal lobe (seizure focus)	24
Ipsilateral basal ganglia	13
Bilateral basal ganglia	2
Ipsilateral thalamus	2
Bilateral thalami	2
Contralateral thalamus	1
Ipsilateral cerebellar hemisphere	1
Contralateral cerebellar hemisphere	1
Contralateral temporal lobe	1

Table 3. SPM in ictal brain perfusion SPECT: areas of hyperperfusion p(FDR) < 0.05.

Brain region	Z score	p (FDR)
Temporal lobe (seizure focus)	5.96	0.001
Contralateral parieto-occipital region	4.30	0.003
Ipsilateral posterior cingulate gyrus	4.22	0.005
Contralateral occipital lobe (calcarine sulcus)	3.64	0.026
Ipsilateral occipital lobe	3.51	0.037
Ipsilateral basal ganglia	3.43	0.046

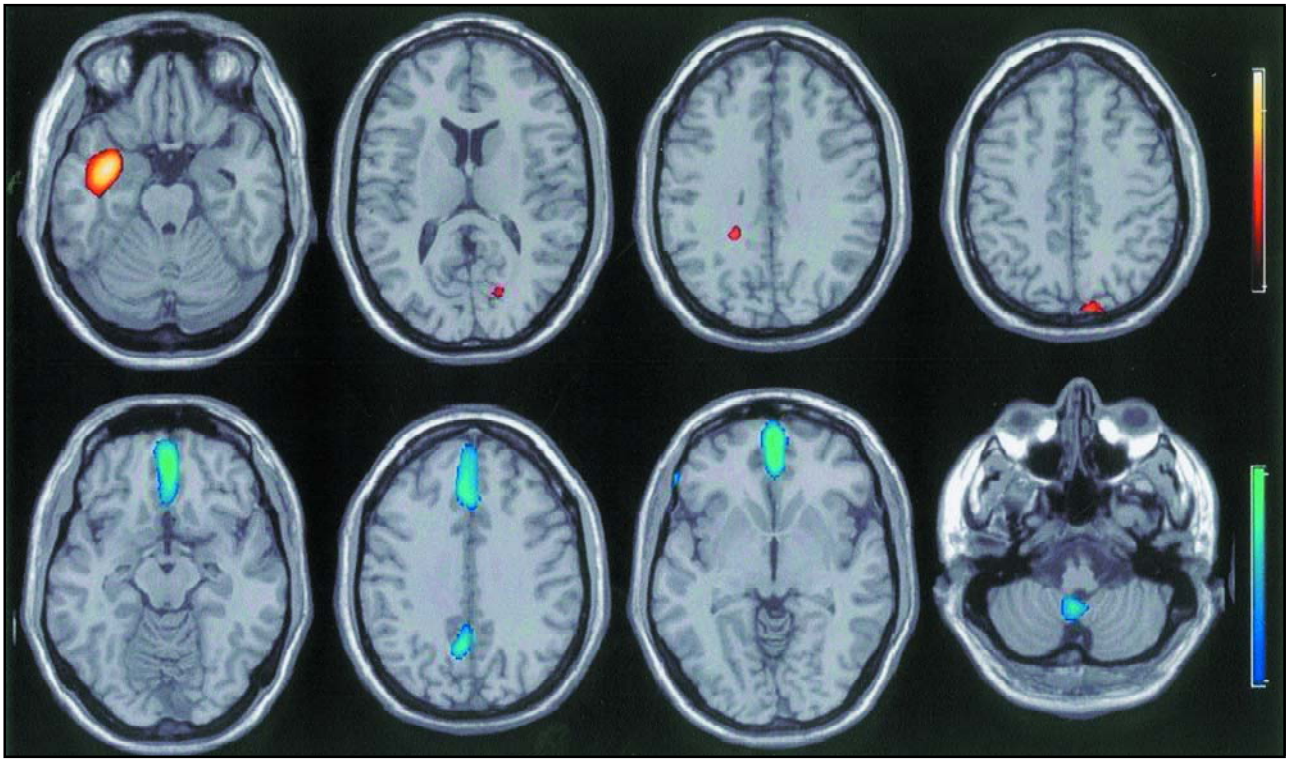

Fig 1. Statistical maps comparing ictal BSI from patients to BSI from neurologically healthy controls. The top row shows the regions with most significant hyperperfusion in orange-red (temporal lobe, contralateral parieto-occipital region, ipsilateral posterior cingulate gyrus and contralateral occipital lobe), while the lower row shows the regions of most significant relative hypoperfusion in blue (bilateral medial frontal lobes, posterior region of cingulated gyrus, lateral region of the ipsilateral frontal lobe and vermis).

Table 4. SPM in ictal brain perfusion SPECT: areas of hypoperfusion p(FDR) < 0.05.

Brain region	Z score	p (FDR)
Medial frontal lobes (bilateral)	4.66	0.009
Posterior region of cingulate gyrus (bilateral)	4.10	0.010
Ipsilateral frontal lobe (lateral region)	4.05	0.010
Vermis	3.88	0.012
Ipsilateral cerebellar hemisphere	3.76	0.014
Ipsilateral orbito-frontal region	3.73	0.015
Contralateral cerebellar hemisphere	3.36	0.029

Interictal SPM – Comparison of the data from contrd participants and patients with TLE did not reveal a significant hypoperfusion on the interictal study at a FDR threshold of p < 0.05.

Ictal SPM – Table 3 displays the SPM ictal BSI findings. Using a p (FDR) < 0.05, the most significant hyperperfusion was found in the temporal lobe (Z score = 5.96) (Figure 1). Hyperperfusion was also noted in the contralateral parieto-occipital region (Z score= 4.30), in the ipsilateral posterior cingulate gyrus (Z score = 4.22), occipital lobes (Z score= 3.64 for the contralateral occipital lobe; Z score = 3.51 for the ipsilateral side) and ipsilateral basal ganglia (Z score = 3.43). Hyperperfusion of the contralateral cerebellar cortex was not observed even when the statistical threshold was reduced to a more liberal p (FDR) < 0.1. Some of these findings are illustrated in Figure.

For a p value (FDR) < 0.01, only three regions of hyperperfusion were observed: the temporal lobe with the highest Z score (5.96), the contralateral parieto-occipital region and the posterior region of the ipsilateral cingulated gyrus.

Regions of relative hypoperfusion were also evaluated (Table 4). A large area of hypoperfusion with the highest Z score, was observed in the medial portion of the frontal lobes bilaterally (Z score= 4.66) (Figure). Hypoperfusion in the posterior portion of the cingulate gyrus (Z score= 4.10), in the

lateral portion of the ipsilateral frontal lobe (Z score = 4.05), the cerebellar vermis (Z score = 3.88), cerebellar hemispheres (Z score= 3.76 ipsilateral hemisphere; Z score = 3.36 for the contralateral hemisphere) and the ipsilateral orbito-frontal region (Z score = 3.73) were also noted.

DISCUSSION

Voxel-based statistical analysis with SPM has been used for analyses of different neuroimaging modalities[10-12]. This method of imaging analyses has the advantage of being fully automated and, therefore, free of operator bias. A previous study using voxel-based morphometry in MRI of patients with mesial TLE showed reduced gray matter concentration in the epileptogenic region (hippocampus), and also in extra-temporal regions such as parahippocampal gyrus, subcortical nuclei, cerebellum, and parieto-occipital regions, suggesting an anatomical route for atrophy[12].

We observed that voxel-wise group analysis of ictal BSIs of patients with TLE reveals significant hyperperfused brain regions that concurs with the region that the electrophysiology study indicates as the seizure onset, i.e., the temporal lobe. Moreover, voxel-wise statistical analysis is able to discriminate hyperperfusion and hypoperfusion regions beyond the anatomic site of seizure onset. Statistical analysis found any regions of perfusion abnormalities when comparing controls to interictal BSI from patients with TLE. This result is in agreement with the literature that has shown a low sensitivity for interictal BSI study alone[3].

In the present study, hyperperfusion in the ipsilateral basal ganglia was noted. This finding has been reported before in qualitative BSI analyses studies[13-15]. These and other regions of hyperperfusion such as the contralateral temporal lobe, the basal ganglia bilaterally and the frontal and parietal lobes have been detected. Increased perfusion in these regions may be due to spread of increased neuronal activity triggered by the epileptogenic focus.

Hyperperfusion of the contralateral occipito-parietal region and the posterior portion of the ipsilateral cingulate gyrus were also noted in the present study. A previous study[6] observed parietal hyperperfusion in a few patients using SPM96 when comparing each individual ictal BSI with their interictal group. These authors believed that the findings of extra-temporal hyperperfusion at a lower threshold could be a false-positive result or a rapid propagation of seizure discharge. In the present group study, hyperperfusion of the contralateral occipito-parietal region and the posterior portion of the ipsilateral cingulate gyrus were clearly observed, probably due to rapid seizure propagation, which is in agreement with the principle of neural networks in epilepsy[16]. These results were observed even when using more rigorous thresholds ($p < 0.01$ with FDR). FDR is a tool that minimizes false positive results, and is not available in previous versions of SPM.

The basal ganglia have many connections with the frontal and temporal lobes and thus hyperperfusion of the basal ganglia is probably secondary to subcortical activation from the cortical focus through corticostriate connections[17,18]. Because of the clustering of corticopontocerebellar fibers in the basal ganglia, activation of the basal ganglia from temporal lobe seizures may stimulate these corticopontocerebellar fibers causing hyperperfusion on the contralateral cerebellar cortex. Hyperperfusion in the contralateral cerebellar hemisphere has been reported in the literature[13,19,20]. Marks, et al.[21] observed that most contralateral cerebellar hyperperfusion occurred contralateral to frontal lobe hyperperfusion. These findings were also observed by Shin, et al.[13]. These authors found that contralateral cerebellar hemisphere hyperperfusion occurred more often in MTLE seizures associated with frontal hyperperfusion. We did not find cerebellar or frontal lobe hyperperfusion. On the contrary, our results showed cerebellar and frontal lobe hypoperfusion, as also observed by Van Paesschen, et al.[22].

In the present study, bilateral occipital lobe hyperperfusion was noted when comparing ictal images to images from control participants. This finding was previously noted by Van Paesschen, et al.[22] during a statistical voxel-wise paired comparison between ictal with interictal BSI. They believed that this finding was explained by a relative occipital hypoactivation during interictal injection with eyes open in a dimly lit environment as opposed to ictal injection that happened in a fully illuminated room. In our study, even though the ictal BSI was compared to a control group and not with the interictal study, the same explanation is valid, due to the fact that radiotracer injection during seizure was performed with the patients' eyes open, in contrast to the control group, who remained in a dark, quiet room. Another hypothesis for occipital hyper-

perfusion could be seizure spread from the epileptogenic focus.

Ipsilateral frontal lobe hypoperfusion has been previously observed by some authors[22-24]. In the present study bilateral frontal lobe hypoperfusion similar to the study of Van Paesschen, et al.[22] was observed. They[22] suggested three possible explanations for this finding: a steal phenomenon, absence of active frontal lobe cognitive process or ictal surround inhibition. They also reported hypoperfusion of the contralateral cerebellar hemisphere, and believed that it could be secondary to a diaschisis related to the ipisilateral frontal lobe hypoperfusion. We found bilateral cerebellar hypoperfusion which was probably related to a diaschisis secondary to the bilateral frontal lobe hypoperfusion.

However, some caution should be noted in interpreting these regions of hypoperfusion. There is clear evidence from EEG and calibrated BSI that neural activity and global perfusion increase during the early phase of a seizure. Yet, in our analysis we calibrated the overall cerebral perfusion levels to be equal across all scans (minimizing variability due to bolus uptake). Therefore, hypoperfusion may be relative to other regions with extremely high levels of ictal perfusion. In addition, the areas of ictal onset and seizure propagation vary across patients and a group analysis may underestimate areas of hyperperfusion. Therefore, the results presented in this study are preliminary and a next step should be an analysis of each individual patient to control group using the FDR method.

We demonstrated that group voxel-wise analysis is able to identify the temporal lobe hyperperfusion associated with seizure onset in patients with TLE. Moreover, we demonstrated that areas beyond the seizure onset zone, which are functionally and anatomically connected to the medial portion of the temporal lobe, also exhibit increased perfusion. This finding is in accordance with the notion that a neuronal network involving the medial portion of the temporal lobe and the limbic system is activated during seizures in patients with MTLE, playing a role in the pathophysiology of the disease[16]. We also observed that significant hypoperfusion occurs in other brains areas that are possibly not recruited, or inhibited by seizure discharges.

In conclusion, a voxel-wise analysis of ictal BSI from a group of patients with TLE, demonstrated a network of distant regions of perfusional alteration which may play active role in seizure genesis and propagation.

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