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Voxel-Based Morphometry in Epileptic Baboons: Parallels to Human Juvenile Myoclonic Epilepsy

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Abstract

The epileptic baboon represents a natural model for genetic generalized epilepsy (GGE), closely resembling juvenile myoclonic epilepsy (JME). Due to functional neuroimaging and pathological differences between epileptic (SZ+) and asymptomatic control (CTL) baboons, we expected structural differences in gray matter concentration (GMC) using voxel-based morphometry (VBM). Standard anatomical (MP-RAGE) MRI scans using a 3T Siemens TIM Trio (Siemens, Erlangen, Germany) were available in 107 baboons (67 females; mean age 16 ± 6 years) with documented clinical histories and scalp-electroencephalography (EEG) results. For neuroimaging, baboons were anesthetized with isoflurane 1% (1-1.5 MAC) and paralyzed with vecuronium (0.1-0.3 mg/kg). Data processing and analysis were performed using FSL's VBM toolbox. GMC was compared between CTL and SZ+ baboons, epileptic baboons with interictal epileptic discharges on scalp EEG (SZ+/IED+), asymptomatic baboons with abnormal EEGs (SZ-/IED+), and IED+ baboons with (IED+/PS+) and without (IED+/PS-) photosensitivity, and the subgroups amongst themselves. Age and gender related changes in gray matter volumes were also included as confound regressors in the VBM analyses of each animal group. Significant increases in GMC were noted in the SZ+/IED+ subgroup compared to the CTL group, including bilaterally in the frontopolar, orbitofrontal and anterolateral temporal cortices, while decreases in GMC were noted in the right more than left primary visual cortices and in the specific nuclei of the thalamus, including reticular, anterior and medial dorsal nuclei. No significant differences were noted otherwise, except that SZ+/IED+ baboons demonstrated increased GMC in the globus pallidus bilaterally compared to the SZ-/IED+ group. Similar to human studies of JME, the epileptic baboons demonstrated GMC decreases in the thalamic and occipital cortices, suggesting secondary injury due to chronic epilepsy. Cortical GMC, on the other hand, was increased in the anterior frontal and temporal lobes, also consistent with human JME studies. This VBM study may indicate a combination of developmental and acquired structural changes in the epileptic baboon.

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Keywords

Genetic generalized epilepsy; Baboon; MRI; Voxel-based Morphometry; Photosensitivity

Brain MRI typically does not reveal any structural abnormalities in people with juvenile myoclonic epilepsy (JME) (Koepp, 2005). Nonetheless, group-wise statistical comparisons using voxel-based morphometry (VBM) do provide evidence for focal structural changes in the brains of people with JME (Woermann et al., 1999). Several studies have confirmed the finding of increased gray matter volumes (GMV) or concentration (GMC) bilaterally in the superior frontal (mesiofrontal) gyri (Kim et al., 2007; Lin et al., 2009). VBM studies in people with JME have also demonstrated increases in GMC elsewhere in the brain, including the medial frontal and orbitofrontal cortices (Lin et al., 2007; Betting et al., 2006). While the significance of VBM changes are still unknown, several authors suggest that increases in gray matter volume or concentration signify cortical developmental abnormalities (Woermann et al., 1999; Lin et al., 2009; Betting et al., 2006). Decreases in VBM were reported bilaterally involving the thalami in two studies (Kim et al., 2007; Lin et al., 2009) and bilaterally the insulae and cerebellar hemispheres in one study (Lin et al., 2009). Decreases in gray matter volume or concentration are thought to reveal cell reduction in the cortical and subcortical structures, probably secondary to seizure-induced cell loss (Kim et al., 2007; Lin et al., 2009).

There is still substantial disagreement on whether there are cortical developmental changes in autopsied people with generalized genetic epilepsies (GGE), some of whom were diagnosed with JME (Meencke and Janz, 1985; Lyon and Gastaut, 1985; Opeskin et al., 2000). A recent MRI study evaluating the direction and magnitude of metric distortion of cortices in JME patients relative to controls demonstrated that surface area and mean curvature – both being measures of cortical folding and markers for developmental anomalies – were more important markers for morphometric differences than cortical thickness (Ronan et al., 2012). In order to better understand the significance of these VBM findings compared to brain histopathological changes, animal models that are adequately characterized by EEG and MRI are needed.

The baboon is a natural model of genetic generalized epilepsy (GGE), with affected animals exhibiting spontaneous generalized myoclonic and tonic-clonic seizures, predominantly in the morning (Killam, 1979; Szabó et al., 2012). Similar to humans, scalp EEG studies in the baboon demonstrate generalized ictal (during seizures) and interictal (between seizures) epileptic discharges (IEDs) (Szabó et al., 2013). These studies also confirmed earlier findings of photosensitivity of the epileptic baboon, implying that visual stimuli, especially flashing lights, can induce seizures and IEDs (Killam, 1979; Szabó et al., 2013). Based upon these electroclinical features, the epilepsy of the baboon closely resembles JME. Earlier morphometric studies evaluating sulcal areas did not demonstrate significant differences between baboons with interictal epileptic discharges (IED+) on scalp EEG, some of which also had a history of witnessed seizure, compared to asymptomatic baboons without interictal epileptic discharges (IED–) (Szabó et al., 2011). Nonetheless, post-hoc comparisons demonstrated significant decreases in sulcal areas in central, intraparietal and

cingulate sulci in the IED+ baboons. Flow cytometry studies comparing two epileptic (SZ+) baboons to asymptomatic control (CTL) baboons demonstrated about 50% reduction in cell and neuron density in the peri-rolandic cortices of the epileptic baboons, with relative sparing of the frontopolar and occipital cortices (Young et al., 2013).

Based upon the preliminary MRI and histopathological findings (Szabó et al., 2011; Young et al., 2013) and human VBM studies (Woermann et al. 1999, Kim et al., 2007; Lin et al., 2009; Betting et al., 2006), we expected the epileptic baboons would demonstrate morphometric differences affecting cortical and subcortical gray matter structures. Because of preliminary evidence of reduced cell and neuronal density in epileptic baboons, we evaluated differences of GMC between SZ+ and abnormal electroclinical subtypes and CTL groups. We were expecting GMC to be increased in the frontal and temporal cortices, and reduced in the perirolandic regions, and reduced in the thalami.

Methods

Animal selection

MRI studies were available for review in 208 (134 female) baboons (*Papio hamadryas anubis* and its their hybrids) with a mean age of 16 $\pm$ 5 years. The baboons were collected from different studies, 180 baboons were scanned as part of a study evaluating heritability of brain structures and volumes (Kochunov et al., 2007; Rogers et al., 2007), and 28 baboons that were scanned as part of two structural or functional neuroimaging studies in epileptic baboons (Szabó et al., 2015; Salinas and Szabó, 2015). There were no neurological exclusion criteria for the first cohort, but all of the baboons selected for the heritability studies had a minimum age of 6 years old, when the baboon brain is fully developed (Leigh, 2004), and the latter groups included baboons with active epilepsy and age-matched controls. Of the original cohort, clinical history and scalp-electroencephalography (EEG) results were available for 148 (101 female) baboons. Of these baboons, 19 (11 female) animals had witnessed spontaneous seizures, six had only ketamine-induced seizures, 31 (17 female) baboons had craniofacial trauma suggestive but not specific for seizure-related injuries, and 70 (54 female) animals were asymptomatic for seizures or craniofacial trauma. We removed 41 baboons from the analyses, including 18 because of evidence of a structural abnormality (mainly colpocephaly) or inadequate neuroimaging quality. The remaining baboons were removed as they belonged poorly defined electroclinical categories, including the baboons with seizures only triggered by ketamine and baboons with craniofacial trauma but otherwise normal EEG studies.

The clinical groups were categorized according to clinical history of seizures and/or craniofacial trauma and scalp EEG findings for the remaining 107 baboons (67 F/40 M) (see Table 1). These subgroups include all SZ+ baboons, SZ+ animals with or without IEDs on scalp EEG (IED+; include asymptomatic baboons, seizure animals and baboons with CFT), animals with IEDs with (SZ+/IED+) or without (SZ-/IED+) seizures, animals with IEDs with (IED+/PS+) or without (IED+/PS-) photosensitivity, and asymptomatic control baboons with normal EEG studies (CTL). All neuroimaging and scalp EEG studies were acquired at the Research Imaging Institute, University of Texas Health Science Center at San Antonio (UTHSCSA). No statistically significant differences were noted between the

comparison groups except for age and gender (SZ+/IED+ vs SZ-/IED+ groups). The SZ-/IED+ was significantly younger (Student t- test, two-tailed, equal variance, $P < 0.02$) and associated with male gender (Fisher Exact Test, two-tailed, $P < 0.02$). Furthermore, total brain volumes were available for 82 baboons from the first cohort (Kochunov et al., 2007; Rogers et al., 2007), where there were no clinical selection criteria for those scans. There was no significant difference of spatially-normalized total brain volumes between any of the diagnostic groups (mean $192 \pm 6 \text{ cm}^3$, Student t-test, two-tailed, $\alpha < 0.05$). The EEG and neuroimaging studies were approved by the Institutional Animal Care and Use Committees of the UTHSCSA and the TBRI. The baboons were treated in strict accordance with the United States Public Health Service's *Guide for the Care and Use of Laboratory Animals* (Institute for Laboratory Research, 2011), the *Animal Welfare Act* (Animal Welfare Act, 2008), and complied with ARRIVE guidelines (<http://www.nc3rs.org.uk>).

Scalp EEG

Surface electrodes are placed according to the standard international 10-20 electrode placement system at FP1, FP2, T8, C4, Cz, C3, T7, O1, O2, A1 and A2 positions. Bipolar montages were utilized for both the recording and review of the EEG data, and included the longitudinal chains FP1-C3-O1, FP1-T7-O1, FP2-C4-O2, and FP2-T8-O2, as well as the transverse chain T7-C3-Cz-C4-T8. Electrodes were also placed bilaterally beside the eyes to monitor lateral eye movements (EOG1, EOG2), over the deltoids or paraspinal muscles to monitor skeletal muscle activity, and a single electrode monitored the heart rhythm (ECG). EEG studies were acquired on a laptop-based acquisition machine (Grass-Telefactor, U.S.A., XLTEK, Canada, and Nihon-Kohden, Japan). Electrode impedances were below 10 k Ω . Ketamine was used to sedate animals in order to transfer them to a primate chair for electrode placement and EEG recording. Ketamine was injected intramuscularly using a mean dose of $5.6 (\pm 0.8) \text{ mg/kg}$, transiently sedating the animal without suppression their respiratory drive. At these doses, ketamine can activate interictal and ictal epileptic discharges, with minimal effect on photosensitivity (Szabó et al., 2013). ILS was performed at least 15 minutes apart, the first time while the baboons were still sedated, and the second time after they were able to track movement in their environment. The same dose of ketamine was administered prior to the baboons' removal from the primate chair. The baboons were recorded for 10 minutes after the second injection for ictal or interictal epileptic discharges acutely provoked by the ketamine (peak dose effect). Almost all of the EEG studies were completed within one hour. The EEG studies were interpreted and classified by a single investigator, who is board certified in clinical neurophysiology and epilepsy (CAS). This investigator was blinded to the animals' previous histories while interpreting the scalp EEG study. The electroclinical classifications were summarized previously (Szabó et al., 2013).

Data acquisition

The MRI scans were performed on a 3T Siemens TIM Trio clinical MRI scanner using a body radio-frequency transmission coil with a 12-channel head RF receiver coil (Siemens, Erlangen, Germany). High-resolution anatomical images were acquired using an MP-RAGE sequence (TR/TE/flip angle = $2100 \text{ ms}/3.1 \text{ ms}/12^\circ$), non-selective inversion pulse, TI = 1100 ms, FOV = $160 \times 192 \times 192 \text{ mm}$, 1.0 mm isotropic spatial resolution. The anesthetized

animal preparation - for optimized physiological stability and functional imaging responses - has been described in previous studies (Szabó et al., 2007; Salinas and Szabó, 2015). Briefly, for each anatomical MRI scan, animals received an injection of intramuscular ketamine (5-10 mg/kg) or diazepam 10 mg for initial sedation, intubation and intravenous catheterization. The baboons were anesthetized with isoflurane 1% (1-1.5 MAC) during acquisition of structural MRI scans. Each animal's respiration, heart rate and oxygenation were monitored throughout the procedures and in the recovery room. No complications were noted during or after any of the procedures.

Data preprocessing

Data processing and analysis were performed using the FMRIB Software Library (FSL) VBM toolbox (Douaud et al., 2007) using an optimized VBM protocol (Good et al., 2001) and FSL tools (Smith et al., 2004). The VBM pre-processing stream consisted of the following steps: 1) each baboon's anatomical MRI underwent manual brain-extraction by an experienced neuroimaging practitioner (FSS) with extensive knowledge of the baboon brain; 2) the brain-extracted MRIs were segmented using FSL's FAST tool, which segmented the brain into cerebrospinal fluid, gray matter, and white matter masks; 3) each baboon's gray matter mask was linearly transformed - using FSL's FLIRT tool - to a representative baboon brain; 4) sixty, randomly chosen gray matter masks (30 CTL, 30 IED+; excluding baboons with colpocephaly or occipital horn elongations) were combined to create a study-specific gray matter baboon template; 5) each baboon's native gray matter mask was then non-linearly transformed to this baboon template image using FSL's FLIRT tool and modulated using the Jacobian of the non-linear warp field; 6) these images were then smoothed with a Gaussian filter (FWHM = 1.15 mm). A general linear model (GLM) was used to compare voxel-wise differences in the gray matter volume between the CTL and EPI group. Non-parametric statistical tests were performed using FSL's "randomise" command with 5000 permutations and threshold-free cluster enhancement. The level of significance in the resulting images was considered using a p -value < 0.05 , corrected for multiple comparisons using the family-wise error rate (Smith and Nichols, 2009). Cluster sizes and locations are listed in Table 2, and correlated with homologous cortical regions using the rhesus brain atlas (Saleem & Logothetis, 2007). The subcortical structures, including the subnuclei of the thalamus and globus pallidus were identified using stereotactic maps of the basal ganglia created from histological preparations of 50 micron thickness (Davis and Huffman, 1968). Statistical parametric maps were prepared for the following group-wise comparisons: SZ+ vs CTL, IED+ vs CTL, SZ+/IED+ vs CTL, SZ-/IED+ vs CTL, IED+/PS+ vs CTL, IED+/PS- vs CTL, SZ+/IED+ vs SZ-/IED+, and IED+/PS+ vs IED+/PS-. Although the age and gender distributions were similar in each animal group, we included them as confound regressors in each VBM analysis.

Results—Significant increases in GMC were noted in the SZ+/IED+ compared to the CTL baboons bilaterally in the anterolateral temporal lobes, lateral orbitofrontal regions, and frontopolar regions (Table 2, Figure 1). Significant decreases were noted in the thalamus bilaterally, affecting the reticular, anterior and mediodorsal nuclei of the thalamus, as well as the right more than left occipitotemporal and calcarine sulci (Table 2, Figure 1). These changes were not accounted for by age at the time of MRI. There were no significant

regional differences of GMC between IED+ and IED−baboons, IED+/PS+ and IED+/PS−, or between any of these subgroups and controls. However, when comparing SZ+/IED+ and SZ−/IED+ baboons, GMC was significantly increased in the globus pallidus bilaterally (Table 2, Figure 2).

Discussion—Similar to juvenile myoclonic epilepsy (JME), voxel-based morphometry (VBM) demonstrates structural changes in the baboon model of genetic generalized epilepsy (GGE). Increases of gray matter concentration (GMC) were noted bilaterally in the frontopolar, lateral orbitofrontal and anterolateral temporal cortices, regions that were also described in people with JME. Decreases in GMC were identified bilaterally in the thalami, a finding that has been reported in people with JME (Kim et al., 2007; Lin et al., 2009). Decreases of GMC in the left lateral geniculate nucleus, right greater than left calcarine and occipitotemporal decreases have not been commonly encountered in VBM studies, except when focusing on JME patients that are photosensitive (Lin et al., 2009). One study demonstrated differences in cortical morphology in the occipital lobes and lingual gyri, but this was not attributed to change in GMC, rather surface morphology (Ronan et al., 2012). Cortical regions with increased GMC or GMV in people with JME that were not altered in the baboons included the mesiofrontal surfaces bilaterally (Woermann et al., 1999; Kim et al., 2007; Lin et al., 2009). Subcortical regions that demonstrated increases in GMC in baboons with seizures compared to those only at risk for seizures were the internal globus pallidus, structures that were not affected in human studies. Overall, VBM in the epileptic baboon may not only provide an excellent structural model for human JME, but could also provide insight into the subcortical modulation of the epileptic networks.

The significance of increased regional gray matter volumes (GMV) or concentrations in human VBM studies is still unclear. It is generally believed that the increased cortical GMV or GMC are markers for a developmental abnormality in people with GGE, caused by an increase of cortical or subcortical neurons. Human VBM studies often reference pathological studies in people with GGE (Meencke and Janz, 1985), particularly JME, suggesting abnormalities of cortical maturation abnormalities or “microdysplasias”, although these findings have been disputed (Lyon and Gastaut, 1985; Opeskin et al., 2000). The pathological findings included increased neurons in the stratum moleculare, subcortical white matter, but also increased neuronal density within the cortices, providing a plausible explanation for the increased GMV or GMC in people with JME. Indeed, the pathologically abnormal brain regions included the frontal poles, lateral inferior frontal cortices and superior temporal gyri (Meencke and Janz, 1985), brain regions that approximated areas identified in the human VBM studies (Lin et al., 2009; Betting et al., 2006). More importantly to our study, the cortical areas identified with abnormal histopathology in humans also overlapped with brain regions demonstrating increased GMC in the baboons. GMC of the globus pallidus was significantly increased in baboons with witnessed seizures (SZ+/IED+) compared to asymptomatic baboons merely at risk for seizures based upon evidence of interictal epileptic discharges on scalp EEG (SZ−/IED+). Why the globus pallidus should be the only basal ganglia reflecting GMC increases is unclear, but this finding may reflect their role of the subcortical networks for seizure modulation. They were the only subcortical regions consistently reflecting activations during H²¹⁵O-PET studies

comparing photic stimulation induced cerebral blood flow (CBF) changes between photosensitive and asymptomatic baboons, more specifically between photosensitive baboons with photically-induced seizures vs interictal epileptic discharges, and demonstrated increased functional connectivity on resting-state functional MRI compared to controls (Szabó et al., 2007; Szabó, Narayana and Salinas, 2011; Salinas and Szabó, 2015). The PET findings may be consistent with previous observations that the globus pallidus belongs to a nonselective subcortical-cortical dopaminergic network activated by seizures, resulting in the modulation or suppression of seizures rather than participating in the epileptic network (Gale, 1992). In this setting, it is possible that GMC increases in globus pallidus of the epileptic baboons reflect acquired hypertrophy or hyperplasia, and not a developmental etiology. Alternatively, increased cell density may represent disrupted tangential neuronal migration from a residual medial ganglionic eminence (de Nijs et al., 2012). EFHC1 mutations, encountered in 9% of people with JME, are presumed to affect microtubule formation necessary for mitosis and neuronal migration, and could arrest inhibitory neurons in the subventricular zone. However, findings of increased functional connectivity in the same regions would not be expected in a residual nest of non-migrating GABAergic neurons (Salinas and Szabó, 2015).

Decreased GMC was noted bilaterally in the thalami of the epileptic baboons, consistent with MRI studies in human JME (Koepp, 2005; Betting et al., 2006; Kim et al., 2007; Lin et al., 2009). The nuclei that are most affected appear to be the reticular thalamic nuclei, anterior and mediodorsal nuclei. The reticular thalamic nuclei play an essential role in the synchronization and sustenance of generalized ictal and interictal epileptic discharges (O'Muircheartaigh et al., 2012). Although the anterior and mediodorsal thalamic nuclei have strong limbic connections, decreased functional and structural connectivity of these nuclei have been demonstrated in human GGE (O'Muircheartaigh et al., 2012; Wang et al., 2012). Therefore, it is likely that the decreases in GMC reflect seizure-induced injury (Betting et al., 2006; Kim et al., 2007; Lin et al., 2009; O'Muircheartaigh et al., 2012). Similarly, GMC was decreased in the primary and secondary visual areas, in addition to the lateral geniculate nucleus. VBM studies in human JME also demonstrated occipital lobe GMC reductions as well as changes in surface area and gyral shapes (Lin et al., 2009; Ronan et al., 2012). These GMC differences, on the other hand, were not noted when comparing IED+ baboons with (IED+/PS+) and without (IED+/PS-) photoparoxysmal responses, or between IED+/PS+ and control baboons. While photosensitivity associated with the epileptic phenotype of the baboon may be the reason for the GMC loss in the visual system, cell loss in the visual system appears to be associated with a history of clinical seizures. The visual cortices are not only involved in the generation of the photoparoxysmal or photoconvulsive responses, but also play an important role in the generation of spontaneous ictal and interictal epileptic discharges in the baboon (Szabó et al., 2012; Szabó et al., 2011).

While VBM findings between baboons and humans demonstrate striking similarities, the broad mesiofrontal GMV or GMC increases reported in human studies were not confirmed in the baboon. Also, in contrast to human studies, we were not able to perform appropriate correlation analyses between regional GMC changes and epilepsy duration to tease out potential seizure-induced cell loss. Unfortunately, the utility of historical factors in the baboon is limited to accidental observation of seizures or craniofacial trauma, and hence

epilepsy onset and severity are not reliable markers. Other shortcomings of this study include insufficient numbers of baboons to demonstrate more pronounced statistical differences, and the structural differences between baboon and human brains, as the smaller brain volumes with proportionally smaller frontal lobes in baboons may limit translatability.

In summary, this VBM study in the baboon confirmed the utility of this animal model for investigation of structural abnormalities and changes affecting the brains of humans with GGE, but particularly with JME. The baboon provides an excellent platform for the evaluation of the congenital and acquired factors impacting the epileptic phenotype. In pursuit of the pathophysiology underlying GGE, there is a need to systematically - both quantitatively and qualitatively - correlate histopathology with MRI findings. Secondly, future neuroimaging studies need to map both changes in structural markers and functional connectivity over during the course the disease.

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Highlights

- This is the first voxel-based morphometry (VBM) study in a baboon model of genetic generalized epilepsy (GGE).
- Pattern of gray matter concentration (GMC) changes resembles those reported in people with juvenile myoclonic epilepsy (JME).
- GMC increases were noted in the anterior frontal and temporal lobes of epileptic baboons.
- GMC decreases were noted in the visual system and selected thalamic nuclei.
- The GMC changes suggest the coexistence of abnormal cortical development and seizure-induced cell loss.

Figure 1. Gray Matter Concentration Differences Between SZ+/IED+ and CTL groups Legend: Red/orange marks regions in which epileptic baboons have decreased GMC, and blue/green where they have increased GMC, Panel A shows a transaxial slice through a three-dimensionally rendered surface, Panel B shows axial cuts through the most affected brain regions.

Figure 2. Gray Matter Concentration Differences Between SZ+/IED+ and SZ-/IED+ Groups
 Legend: Red/orange identifies regions overlapping the internal globus pallidus, where SZ +/IED+ baboons have increased GMC.

Table 1
Characteristics of Clinical Groups

Groups	Number	Gender	Age at scan (yo)	Associated MRI Variants
IED+ (total) *	67	41 F/26 M	17+/-6	11 OH elongation 4 TH enlargement 1 BG calcification
SZ+/IED+	19	11 F/8 M **	14+/-6 **	2 OH elongation
SZ-/IED+	29	24 F/5 M **	18+/-6 **	7 OH elongation 4 TH enlargement 1 BG calcification
IED+/PS+	34	19 F/15 M	17+/-7	4 OH elongation 3 TH enlargement 1 BG calcification
IED+/PS-	34	22 F/12 M	16+/-5	7 OH elongation 2 TH enlargement
CTL	40	26 F/14 M	16+/-5	9 OH elongation 2 TH enlargement

Legend: IED interictal epileptic discharges, IED+ scalp EEG positive for IEDs, IED- no IEDs on scalp EEG, SZ+ history of witnessed seizures, SZ - no history of witnessed seizures, PS+ positive photosensitivity on scalp EEG, PS- no photosensitivity, the IED+ group also includes baboon with no available clinical history (N=2) and baboons with craniofacial trauma but no witnessed seizures (N=21), yo years old, F(emale), M(ale), OH occipital horn, TH temporal horn, BG basal ganglia,

* includes baboons with seizures, without seizures, and craniofacial trauma only,

** statistically significant differences.

Table 2
Maximum cluster locations of the VBM differences between the respective baboon groups

Electroclinical Groups	Max Cluster Location	Label *	Max Cluster Z-score	Cluster Size (voxels)	Location (mm)		
					X	Y	Z
SZ+/IED+ > CTL	Lateral Orbital Gyrus	Area 12o	5.39	5176	29.5	16	-8
	Lateral Orbital Gyrus	Area 12o	5.90	1167	-24.5	22.5	-18
	Medial prefrontal cortex	Area 10m	6.44	612	-5	40.5	-1
	Medial prefrontal cortex	Area 10m	4.95	535	4.5	39.5	-1.5
	Postcentral Gyrus	Area 3a/b	5.40	178	-29	17.5	-5.5
	Superior Temporal Gyrus	A1	3.80	60	29	13.5	-13.5
SZ+/IED+ < CTL	Occipital Gyrus	V1	5.60	1113	10	-27.5	2
	Thalamus	NA	4.18	331	-4.5	3	0
	Thalamus	NA	3.97	122	2.5	3	1.5
	Lateral Geniculate Nucleus	LGN	4.16	65	-10	-7.5	0
SZ+/IED+ > SZ-/IED+	Globus Pallidus (externa)	GPe	6.36	684	-5.5	12	-10.5
	Globus Pallidus (externa)	GPe	5.48	379	5.5	11	-10

Legend:

* Labels correspond to the homologous cortical regions listed in the rhesus brain atlas (Saleem & Logothetis, 2007). IED interictal epileptic discharges, IED+ positive for IEDs, IED- no IEDs, SZ+ history of seizures, SZ- no history of seizures, PS+ positive photosensitivity, PS- no photosensitivity.