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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 pallidae bilaterally compared to the SZ-/IED+ group. Similar to human studies of JME, the epileptic baboons demonstrated GMC decreases in the thalami 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.

1. Introduction

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., 2009; 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).

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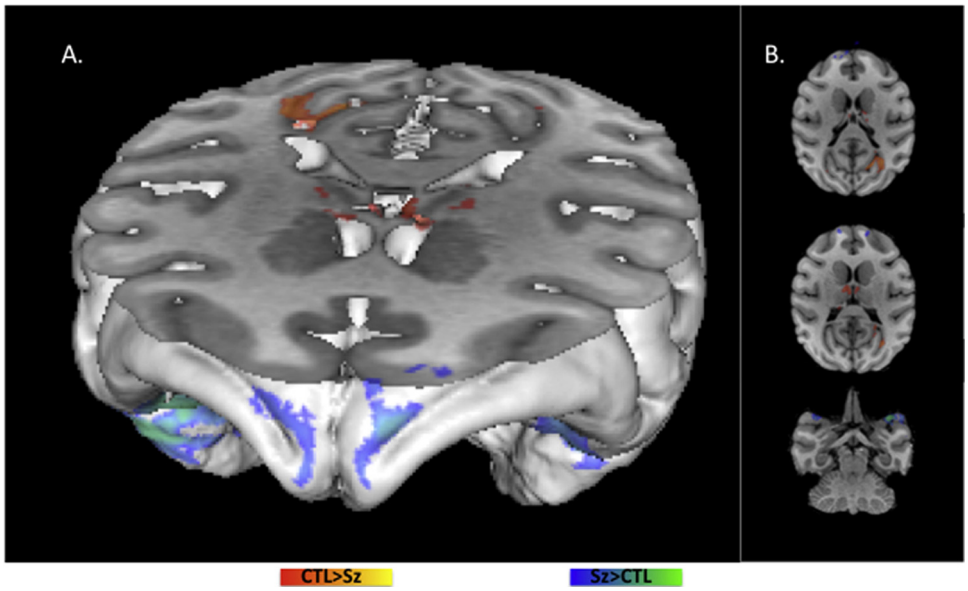

Fig. 1. Gray Matter Concentration Differences Between SZ+/IED+ and CTL groups. Legend: Red/orange marks regions in which epileptic baboons have decreased GMC, and blue/green where they have increased GMC, Panel A shows a transaxial slice through a three-dimensionally rendered surface, Panel B shows axial cuts through the most affected brain regions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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., 2012a). 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., 2011a). 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., 2011a; 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.

2. Methods

2.1. 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+/− 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