fMRI of Absence Seizures in Marmoset Monkeys

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Introduction

A typical absence seizure is manifested behaviorally as a "staring spell" and can be accompanied by atonic postures and automatisms. Children may have 10 to 200 of these seizures in a day and in the more severe case of absence status epilepticus the seizures are unremitting and can last for hours. The incidence of absence seizures in the United States is 1.9 to 8 per 100,000 usually occurring in children between the ages of 4 years and adolescence.

In order to elucidate the brain mechanisms underlying this disorder, a non-human primate model of absence epilepsy was developed, which could be used for awake functional imaging. It has previously been shown that primates have the ability to produce an EEG that mimics the human condition, with a 3 Hz SWD. Marmoset monkeys (*Callithrix jacchus*) were treated with γ-butyrolactone (GBL) to induce absence seizures during blood-oxygenation-level-dependent (BOLD) fMRI. Our hypothesis, based on previous electrophysiology and imaging studies, predicted an increased BOLD signal in the corticothalamic circuit, which many believe to be the source of the SWDs characterizing absence epilepsy.

Methods

Five marmosets were implanted with subcutaneous EEG electrodes and secured in a MR compatible restrainer (Insight Neuroimaging Systems, Worcester, MA). EEG recording, with the animal in the magnet, was accomplished by using nonmagnetic electrodes and battery operated electronics. All images were acquired using a 4.7T/40-cm horizontal magnet interfaced to a Paravision console (Bruker Medical Instruments, MA). Anatomical data sets were acquired using a fast spin echo (RARE) sequence (TR=2.5s; TE=56ms; echo train length=8; field of view=3x3cm; data matrix=256x256; slice thickness=1.5mm). Functional images were acquired using a spin echo (RARE) sequence (TR=2.4s; TE=8ms; FOV=3x3cm; matrix=64x64; slice thickness=1.5 mm; number of slices=18; averages=2). Eighteen contiguous functional images were acquired in 20 seconds and each image acquisition included 15 sets of images for a total acquisition time of 5 minutes.

fMRI was interspersed with EEG recordings due to imaging artifacts which obscured the waveforms. A baseline period was followed by vehicle (saline) and GBL injections. Regions of interest (ROIs) were identified in the cortex and thalamus and analyzed for changes in BOLD signal intensity. STIMULATE software was used to generate an activation map by performing statistical comparisons of control periods to seizure periods with the Student's paired t-test.

Results

Figure 1 is a representative EEG recording following injections of vehicle (saline) and 200 mg/kg GBL. SWDs with a frequency of 3 Hz were found to occur approximately 15 minutes after GBL injection. Figure 2 is an activation map showing the regions in which BOLD signal increases are occurring during 3 Hz SWD formation. The colored pixels indicate the statistically significant ($p<0.05$) pixels determined by t-test analysis and overlaid onto the corresponding anatomy of four consecutive brain slices. The top row, showing no activated pixels following saline injection, indicates the ROIs used for analysis (blue – thalamus, red – frontal gyrus, green – precentral gyrus, yellow – post-central gyrus, purple – superior/medial temporal gyrus). The bottom three rows are activation maps, acquired during seizure activity, at the times shown on the left.

Discussion

Using the BOLD fMRI technique we have shown that the corticothalamic circuit, previously implicated in the pathophysiology of absence seizures, shows robust positive BOLD signal. This activation correlates with the onset of the 3 Hz SWDs that characterize childhood absence epilepsy. The current study has demonstrated the feasibility of using the common marmoset as the most accurate animal model of this generalized epilepsy. This model can now be used to investigate antiepileptic mechanisms of action as well as contribute to the understanding of epilepsy-related effects on learning and memory.

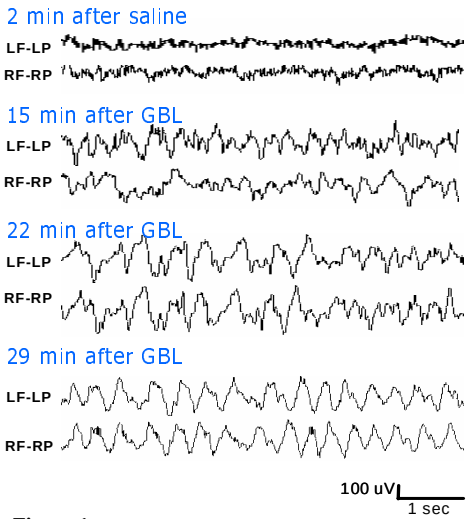

Figure 1.

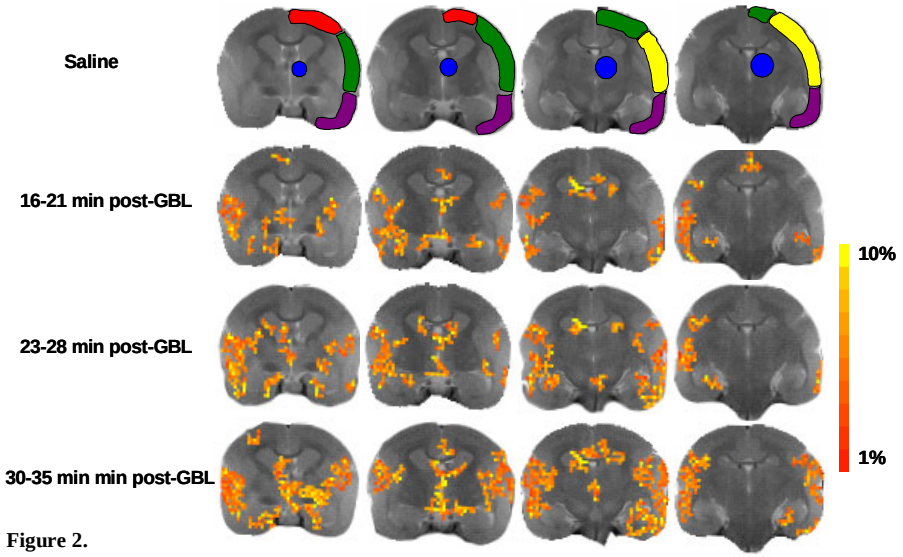

Figure 2.