Original article

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Typical childhood absence seizures are associated with thalamic activation

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ABSTRACT – Functional MRI with simultaneously acquired EEG (fMRI/EEG) can identify areas of signal change associated with interictal discharges. We report the fMRI/EEG study of a child with newly-diagnosed IGE, performed prior to the start of antiepileptic medication. The 7-years-old girl had very frequent absences, associated with eyelid myoclonia. Her EEG showed frequent, typical 3/sec discharges. Functional MRI was performed with a 3T scanner using whole brain gradient echo-planar imaging, and the EEG was recorded with 18, non-metallic, scalp electrodes. Ten bursts of generalized discharges were captured during 30 minutes fMRI/EEG acquisition. The bursts lasted 3.4 (SD ± 0.6) seconds. Event-related analysis was performed with SPM2 and iBrain™ software. Functional MRI showed prominent, bilateral thalamic activation, and less pronounced areas of cortical activation and deactivation. This study demonstrates thalamic activation in typical, untreated childhood absence epilepsy. The cortical signal change may be related to a thalamo-cortical circuit.

Key words: idiopathic generalized epilepsy, functional MRI, thalamus, absence seizure

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Idiopathic generalised epilepsy (IGE) consists of a group of epilepsy syndromes with characteristic seizure and EEG pattern. The seizure onset is typically during childhood or adolescence, and there are normal neurodevelopmental milestones and neuroimaging. The patients have one or several different seizure types, including absences, myoclonus and generalized tonic clonic seizures. The seizure types and the onset of the seizures are commonly used to classify the different types of IGE. The EEG shows characteristic ictal and interictal features, with generalised spike and waves (GSW) and polyspike waves occurring from a normal background (Gloor, 1968). In general, IGE is easily controlled by antiepileptic medication, and the seizures may disappear by adulthood.

Functional magnetic resonance imaging (fMRI) with simultaneous EEG (fMRI/EEG) is a novel, non-invasive technique, suited to localise neuronal activity associated with the interictal discharges observed on the EEG recorded during scanning. fMRI measures the blood oxygenation level-dependent (BOLD) response related to neuronal activation (positive BOLD) or deactivation (negative BOLD). Recently, three papers have studied IGE patients with different methods of combined fMRI and EEG. Archer *et al.* in 2003, documented in five IGE patients, significant BOLD deactivation

in the posterior cingulate without consistent areas of BOLD activation (Archer et al., 2003). Whereas this study used a spike-triggered method, two other reports used continuous fMRI/EEG and event-related analysis. Salek-Haddadi *et al*. described a patient with intractable juvenile absence epilepsy. They found marked bilateral thalamic activation and cortical deactivation during prolonged absences (Salek-Haddadi et al., 2003). Aghakhani *et al*. studied 15 subjects with different subtypes of IGE. They found a mixed pattern with fMRI activation or deactivation, widespread in the cortex, and bilaterally in the thalamus (Aghakhani et al., 2004). Common to all three papers is that the included subjects show somewhat atypical features of IGE; they were adults and had drug-refractory IGE, and particularly in the ictal study the discharges were unusually long, so that atypical absences cannot be excluded. Here, we report the fMRI/EEG study of a child with newly-diagnosed IGE, performed prior to the start of antiepileptic medication.

Materials and methods

Case report

The girl was born one month premature by Caesarean section, as her mother had pre-eclampsia. She was well at birth, and developmental milestones were within normal limits. She had no febrile convulsions, no history of brain injury or other risk factors for the development of epilepsy. There was no family history of epilepsy.

At the age of 7 years, she started having stereotypical events at a frequency of at least twice per hour, at times, up to 30 per hour. During these events, the child was suddenly looking up, and had eyelid fluttering lasting for 5-10 seconds. There was no colour change of her face, no automatisms, and she was unresponsive at the time. There were no reported myoclonic jerks, and apart from a questionable event at the age of 3 years, no indications of generalized tonic clonic seizures.

Her routine EEG at the age of 7 years showed very frequent bursts of bilaterally symmetrical, generalised, approximately 3-Hz fast spike wave and polyspike wave activity, arising from a normal background. Nearly all the bursts were associated with clinical absences and eye blinking. Neurological and physical examination, as well as structural MRI were normal. The fMRI/EEG examination was performed prior to starting antiepileptic medication. The study was approved by the Austin Health Human Research Ethics Committee.

FMRI/EEG methods

MRI imaging was performed using a 3-tesla GE Signa Horizon LX scanner (General Electric, Milwaukee, WI, USA). Gradient echo-planar imaging (EPI) sequences were used, with whole brain coverage (22 axial slices, 4 mm thick, 1 mm gap), 128x128 matrix, 24x24 cm FOV, 60° flip angle, TE 40 ms, TR 3.0 seconds.

The fMRI/EEG was acquired using an MR-compatible EEG system as previously described by our group (Federico *et al.*, 2005, Archer *et al.*, 2003). In brief, 18, non-metallic scalp electrodes connected to carbon fibre leads are applied based on the 10/20 system. Additionally, two chest electrodes were used to record the ECG. The EEG leads were twisted in pairs immediately on leaving the scalp and were held stable with a plastic tube. The signal from the head-box is transferred back to the control room via fibre-optic leads (Archer *et al.*, 2003). The EEG was recorded during the whole examination period. Our system allows for obtaining on-line EEG of a quality sufficient to detect the GSW, however, the quality of the EEG was further improved by Fourier-filtering offline. *figure 1* shows a generalized burst for this patient, as recorded during functional MR scanning. Simultaneous fMRI/EEG was acquired for 30 minutes with the patient at rest. No activation procedures were performed. The discharges identified during scanning had the same morphology as the discharges identified during a resting EEG, recorded immediately prior to the scanning. The bursts, which occurred during this out-of scanner recording, were all associated with a clinical absence and eye-lid myoclonia; therefore it can be assumed that the similar bursts occurring during scanning were also clinical absences.

Functional MRI analysis was performed using SPM2 (www.fil.ion.ucl.ac.uk/spm/) in combination with iBrain ™ (www.brain.org.au/iBrain). The spike-wave discharges on the EEG trace were independently identified by two neurologists (AL and RSB), the onset and duration of each burst were noted. Based on these timings, an event-related analysis was performed, using a canonical haemodynamic response function (HRF). Global intensity normalization was not performed. Correction for multiple comparisons was based on a correction for family-wise-error (FWE) using the theory of Gaussian random fields. However, this correction may be overly stringent, particularly for analysing a single subject. Therefore, the result was also examined using a more lenient threshold with adjustment for false discovery rate (FDR).

Results

Ten bursts of generalized, high voltage, rhythmic GSW were captured during the 30 minutes recording. The bursts lasted an average of 3.4 (standard deviation ± 0.6) seconds.

The fMRI analysis demonstrated a pronounced BOLD response, significant at the most stringent threshold of 0.05, corrected for FWE (*figure 2*A). There was prominent activation in the thalamus bilaterally, with some additional areas of activation in associated white matter tracts. There was little signal change in cortical areas. Assessed at

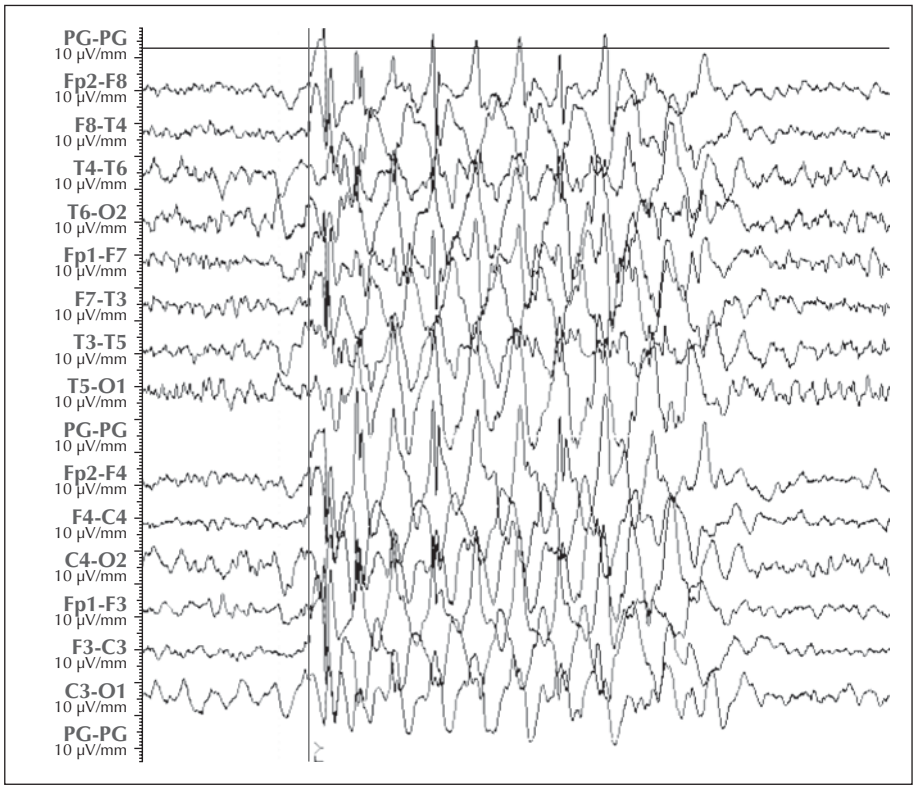

Figure 1. The figure shows a representative section of the EEG recorded during scanning at a time of a burst of rhythmic activity. The EEG was acquired using the 10/20 electrode placement scheme, without the P3 and P4 electrodes. This burst had a duration of 2.4 seconds. The EEG is displayed as seen during fMRI scanning without post-processing. Note the high quality of the on-line EEG, which clearly allows the appreciation of the burst.

a more lenient threshold (FDR), the cortical signal change is more obvious (*figure 2*B). Areas of activation involved the motor cortex bilaterally, and white matter tracts such as the longitudinal fascicle and the optic radiation. Areas of deactivation were found in the right middle frontal gyrus and bilaterally in the retrosplenial areas.

Discussion

We demonstrate highly significant blood-oxygenation level-dependent (BOLD) activation of the thalamus during short absence seizures in a child with newly diagnosed, untreated IGE using fMRI/EEG. This study confirms the findings of Salek-Haddadi *et al.* who found marked bilateral thalamic activation during prolonged absences in an adult with intractable juvenile absence epilepsy (Salek-Haddadi *et al.*, 2003). Thalamic signal change has also been observed in 80% of patients included in a series of adults with refractory IGE (Aghakhani et al., 2004). Our observation extends this finding to a child with typical, untreated IGE and short absence seizures.

The activation of the thalamus during absences fits well with the current experimental and theoretical knowledge of the generation of generalized spike-wave discharges. Several models have been developed to explain the EEG features and clinical characteristics of absence seizures. Penfield proposed the "centrencephalic theory" where the 3 Hertz GSW generator is located in deep midbrain structures, and Gloor suggested thalamus and hyperexcitable cortex as the generator of the rhythmic GSW (Gloor, 1968). Experimental models using depth electrodes have confirmed that GSW can be detected in the thalamus as well as in the cortex (Snead *et al.*, 1999). With the advent of functional neuroimaging during absences, the theoretical models could be directly investigated. Positron emission tomography (PET) has been used with the tracer $H2^{15}O$ to measure cerebral blood flow (Prevett *et al.*, 1995). PET FDG showed diffusely increased glucose metabolism without predominance of any cerebral areas, while PET $H2^{15}O$ indicated thalamic blood flow changes (Prevett *et al.*, 1995). This was complemented by a recent ictal single photon emission computed tomography (SPECT) study (Nehlig *et al.*, 2004). During a prolonged absence seizure, they observed diffuse decrease in cortical blood flow, with relative sparing of the thalamus (Nehlig *et al.*, 2004).

Our results show areas of BOLD increase as well as BOLD decrease. The relationship between BOLD signal changes

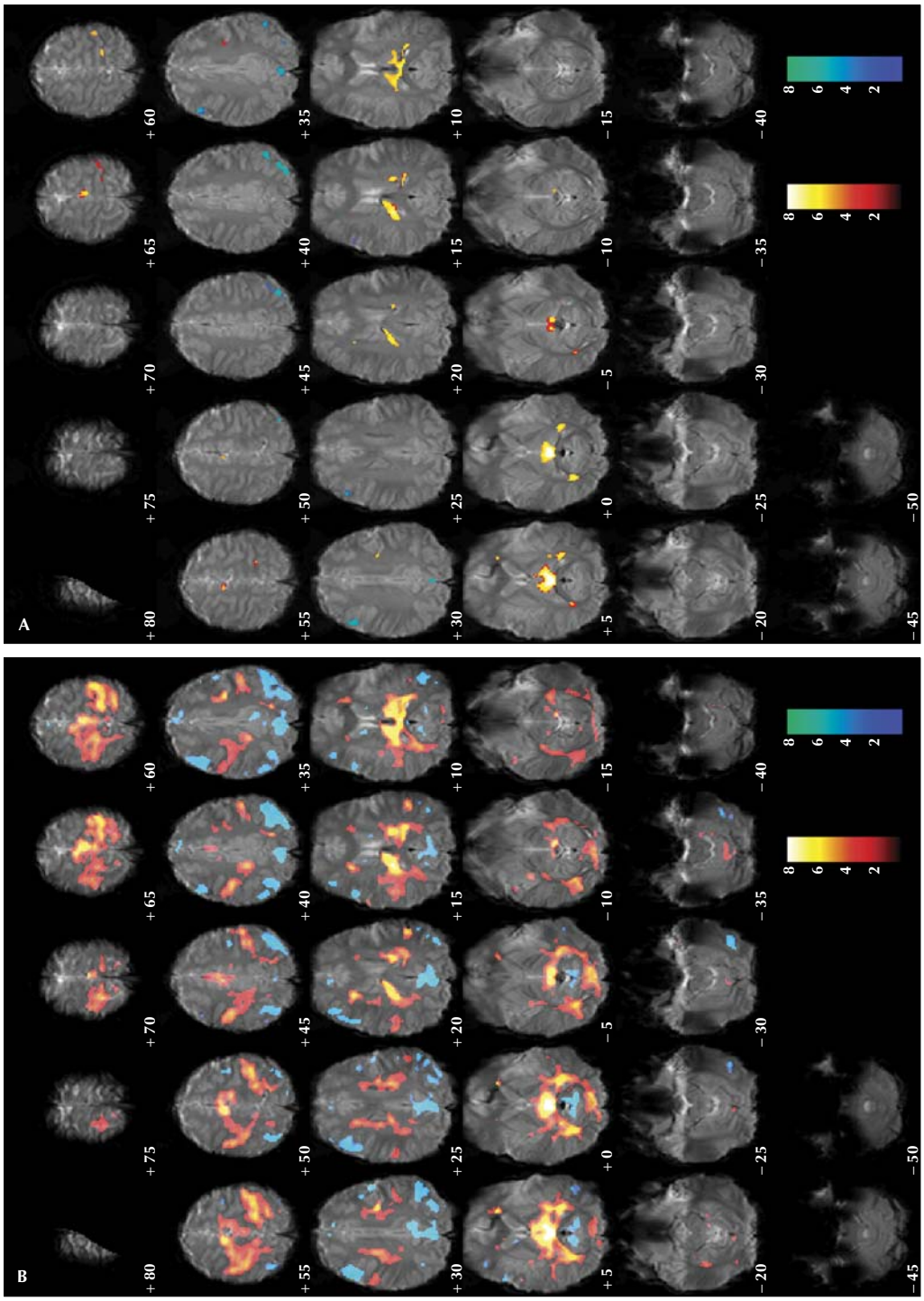

Figure 2. The figure shows the result of the event-related fMRI analysis, based on the timings of the discharges on EEG. Display is in radiological convention (image left is subject's right). The data were analysed using SPM2, areas of activation shown in warm colours, areas of deactivation in cold colours. The color-scale indicates the degree of activation. **A**) Threshold is $p < 0.05$, corrected for multiple comparisons at a FWE false positive rate. Note the prominent activation in the thalamus bilaterally (midline activation, image +5 and +0), with little additional areas of activation in white matter tracts (lateral activation, images +20 and +0), and in the left motor area (image +60). **B**) The same data displayed at a statistical threshold of $p < 0.05$, adjusted for whole-brain false discovery rate. Activation in the thalamus is prominent (yellow-white areas on images -5 to +15). Activation besides the thalamus is now clearly visible. This activation involves the motor cortex bilaterally (images +50 to +65), and deep white matter tracts such as the longitudinal fascicle (+25) and the optic radiation (posterior activation on images +0 and -5). Areas of deactivation are found in the right middle frontal gyrus (images +35, +30) and bilaterally in the retrosplenial areas (images +20 to +40).

and excitatory and inhibitory processes is complex (Arthurs and Boniface, 2002). Increased neuronal activity (which may have excitatory or inhibitory distant effects) in an area of the brain, is associated with a predictable rise in cerebral blood flow, which alters the local fMRI signal (Malonek *et al.*, 1997). The negative BOLD response (*i.e.* a reduction in BOLD signal) is understood to reflect the haemodynamic and metabolic down-regulation accompanying neuronal inhibition (Stefanovic *et al.*, 2004). Our findings suggest involvement of both thalamus and cortex at the time of the absence. Analysed at a restrictive statistical threshold (FWE, controlling the chance of one or more false positives anywhere, *figure 2*A), only the thalamic activation would have been recognized. Application of more recent analysis tools that facilitate adjustment for false discovery rate (controlling the proportion of false positives, (Genovese *et al.*, 2002) (*figure 2*B) showed associated areas of cortical and subcortical activation and deactivation, which may be functionally important for seizure generation and clinical manifestations. The activation in the motor cortex bilaterally may reflect the motor component of the absence seizure, whereas the activation in the white matter tracts may be involved in the rapid propagation of the electrical activity. Areas of deactivation were found in the right middle frontal gyrus and bilateral in the retrosplenial areas. The middle frontal gyrus is involved in working memory processes and the retrosplenial areas in maintaining awareness. The deactivation in these two brain areas may indicate relative inhibition during generalized discharges, as previously discussed (Archer *et al.*, 2003). Absence seizures are characterized by blank staring; these clinical symptoms may be related to transient inhibition of brain areas important for maintaining awareness. □

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