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Cortical and thalamic resting-state functional connectivity is altered in childhood absence epilepsy

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Summary
Purpose: Functional imaging studies have identified a common network of brain regions that activate and deactivate during the generalised spike wave (GSW) discharges of childhood absence epilepsy (CAE). Functional connectivity within this network is also altered during the resting state. In this study our aim was to assess functional connectivity throughout the whole brain of patients with CAE.
Methods: We studied a group of eleven patients with untreated CAE and eleven matched controls using resting-state fMRI. We measured functional connectivity between every pair of voxels and generated images of ''whole-brain'' functional connectivity by counting the number of functional connections of each voxel.
Key findings: There were marked differences between CAE patients and controls in whole brain functional connectivity. The patients had decreased connectivity in the thalamus and basal ganglia and increased connectivity in the medial occipital cortex.
Significance: These findings suggest enduring changes in function of the thalamus and the cortex in CAE patients even when there is no GSW activity. These human functional connectivity data support the findings in animal models of involvement of cortex as well as thalamus in absence epilepsy.

Introduction

Genetic (previously idiopathic) generalised epilepsy (GGE) (Berg et al., 2010) is characterised by episodic brain dysfunction involving widespread hypersynchronous activity appearing as generalised spike wave (GSW) discharges on the EEG (Blumenfeld, 2005). The network of brain regions that are active at the time of these events has been defined using simultaneous EEG and functional magnetic resonance imaging (EEG-fMRI) (Archer et al., 2003; Gotman et al., 2005; Hamandi et al., 2006; Moeller et al., 2008; Carney et al., 2010; Bai et al., 2010). These studies have shown relative increases in the thalamus and decreases in the ''default-mode'' cortical regions, the caudate nucleus and brainstem (herein referred to as the ''GSW network''). In

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addition to these paroxysmal events, GGE patients also show increased cortical excitability (Badawy et al., 2007) and mild ongoing cognitive impairments (Pavone et al., 2001; Henkin et al., 2005), which suggest that the activity and function of brain networks may also be affected during the baseline state between GSW events.

Functional connectivity describes the relationship between different regions of the brain that network together to perform a common function (Friston, 1994). Functional connectivity can be estimated non-invasively with fMRI by measuring the correlation between spontaneous low-frequency haemodynamic fluctuations in different brain regions (Biswal et al., 1995), which has been linked to the synchronisation of slow fluctuations in underlying neuronal networks (Shmuel and Leopold, 2008). Functional connectivity has been shown to be significantly correlated with disease state (Greicius et al., 2004; Cherkassky et al., 2006; Waites et al., 2006) and task performance (Hampson et al., 2006), and is therefore suggested to be a marker of the integrity and efficiency of the brain's functional networks. For example, reduced functional connectivity in the language network has been reported in patients with temporal lobe epilepsy (TLE) (Waites et al., 2006). It is known that TLE patients have atypical language lateralisation (Janszky et al., 2003; Sveller et al., 2006) and language deficits (Howell et al., 1994; Hermann et al., 1997; Field et al., 2000), hence reduced functional connectivity may reflect re-organisation and impairment of language function in these patients.

Several recent studies have investigated the resting-state functional connectivity of specific functional networks in patients with GGE and reported a number of differences in comparison to healthy subjects (Luo et al., 2010; Bai et al., 2011; Killory et al., 2011). These studies have shown functional connectivity decreases in the ''default-mode'' regions (Luo et al., 2010), pair-wise functional connectivity increases between the left and right orbitofrontal cortex (Bai et al., 2011) and reduced connectivity in an ''attentional'' network (Killory et al., 2011). In this study we extended upon these previous reports by investigating functional connectivity throughout the whole brain rather than within a priori selected networks of interest. We acquired resting-state fMRI in a cohort of patients with childhood absence epilepsy (CAE) and age-matched healthy control subjects, measured the functional connectivity between all pairs of voxels, and applied a whole-brain network analysis (van den Heuvel et al., 2008) to identify brain regions with different functional connectivity between the two groups.

Methods

Subjects

Patients were recruited through the EEG Departments of the Austin Hospital and the Royal Children's Hospital in Melbourne. With the consent of subject's parents and their treating clinician, medication was withheld until after the research scan was performed (less than 2 weeks). Scans were performed without sedation. The selection criteria for inclusion in this study were: onset of absence seizures before age ten; absence as exclusive seizure type at time of study; not currently treated; normal background on routine EEG; 3—3.5 Hz GSW during absence; normal early developmental milestones; and normal structural imaging on T_1 and T_2-weighted anatomic MRI. Eleven CAE patients (5 male) meeting these criteria were recruited. The patients were aged from five to fourteen years (mean: 8.7; standard deviation: 2.62). One patient was initially placed on carbamazepine for less than a week. Three patients had previously been treated for absence seizures and had medications ceased following a period of seizure freedom and were studied before treatment was recommenced. A summary of the patients is provided in Table 1, and the cohort is described in more detail in Carney et al. (2010).

Table 1 Patient details.

Age (years)	Age at onset (years)	Sex	Previous medication
5	4	F	None
7	6	F	None
7	7	M	None
7	4	M	VPA/LTG
7	6	F	None
8	8	M	None
9	5	F	VPA
9	4	M	VPA
9	8	F	None
11	9	F	None
14	8	M	CBZ

Abbreviations: CBZ, carbamazepine; LTG, lamotrigine; VPA, sodium valproate.

Eleven healthy control subjects (7 male) were retrospectively selected from a database of subjects who have undergone resting-state fMRI scanning at the Brain Research Institute. The controls were selected to provide as close an age distribution to the patient group as possible, and were aged from seven to twelve years (mean: 8.91; standard deviation: 1.16).

All subjects provided written informed consent and this study was approved by the Human Research Ethics Committee at Austin Health and the Royal Children's Hospital.

Imaging

The fMRI images were acquired on a 3 T GE Signa LX scanner using a BOLD-weighted (Ogawa et al., 1990) gradient-echo EPI sequence. Subjects were scanned in a task-free ''resting-state'' condition. As a consequence of the retrospective selection of control subjects for this study, the two groups were scanned using the following different scanning parameters. The patient scanning parameters were: 40 slices, 3.2 mm thick (+0.2 mm gap); TR = 3200 ms; TE = 40 ms; FOV = 22 cm; matrix = 64 × 64; and the control scanning parameters were: 25 slices, 4 mm thick (+1 mm gap); TR = 3000 ms; TE = 40 ms; FOV = 24 cm; matrix = 128 × 128.

Simultaneous EEG recordings were obtained during the patients' scanning session using a custom-built amplifier and filtering to remove ballistocardiogram and movement artefacts (Masterton et al., 2007). Electrodes were positioned in the standard 10—20 locations (with the exception of Fz). Two experienced electroencephalographers (P.C. and D.F.) reviewed the EEG off-line to identify GSW discharges and perform sleep state classification.

Data analysis

For each subject one-hundred whole-brain volumes were used for the functional connectivity analysis. For the patients we selected periods of ''baseline'' brain activity — defined as a continuous epoch with no GSW detected on the within scanner EEG. We required that each period of baseline be preceded by a minimum of 30 s and fol-