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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-

lowed by a minimum of 10 s of GSW-free EEG. If we could not identify a single continuous baseline of sufficient duration, we created a composite dataset by concatenating shorter baseline periods (Fair et al., 2007) — with the requirement that each such sub-section was of a minimum of 2 min continuous duration. For the control subjects, the analysis epoch began after an initial 5 min of resting-state scanning as an effort to balance for potential habituation effects in the patient group where the selected analysis epochs were spread throughout the scanning session.

The fMRI data were pre-processed with SPM8 software (www.fil.ion.ucl.ac.uk/spm). The following pre-processing steps were used: slice-timing correction, realignment to correct for subject motion, spatial normalisation into MNI space, re-sampling to 3 mm isotropic voxels, and spatial smoothing with a Gaussian kernel (FWHM = 8 mm). The pre-processed images were also filtered to reduce the effects of physiological noise. Noise components were modelled based upon the estimated motion realignment parameters and the average signals within white matter and cerebrospinal fluid (CSF) compartments (Fox et al., 2005). The CSF and white matter compartments were defined using a pair of manually generated mask images containing only voxels with minimal likelihood of grey-matter partial-volume-effects as judged by reference to the group mean fMRI image and a priori probabilistic tissue maps supplied with the SPM8 software. These time-courses modelling physiological noise were entered into a multiple linear regression to estimate their contribution to the fMRI signal at each voxel, and then removed from the data using a weighted subtraction. In contrast to the approach of Fox et al. (2005), the average whole-brain signal was not used in the estimation of physiological noise. This was excluded in consideration of the well established role of the thalamus in absence epilepsy (Blumenfeld, 2005), and observations that the whole-brain signal shows high correlation with the thalamus (Zhang et al., 2008) and its removal from the data can therefore lead to underestimation of thalamic functional connectivity. Finally, each voxel time-course was band-pass filtered (0.01—0.1 Hz) (Biswal et al., 1995) using a discrete Fourier transform.

Functional connectivity was measured in each subject by comparing all pairs of within-brain voxels. The existence of a connection between two voxels was inferred if the Pearson's correlation coefficient between their time-courses was greater than 0.6. A voxel pair was considered functionally connected at the group-level if the average correlation coefficient across subjects exceeded the threshold of 0.6. A relatively high correlation threshold was chosen to reduce the likelihood of including correlations due to residual physiological noise, particularly because the whole-brain average signal was omitted from the noise estimation process, which tends to result in higher inter-voxel correlation coefficients (Murphy et al., 2009).

The functional connectivity measurements were summarised using degree centrality (van den Heuvel et al., 2008). Degree centrality counts the number of functional connections (i.e. $r > 0.6$) at each voxel (the ''degree''), which provides a single value for each voxel representing how connected that voxel is with the rest of the brain, and can be viewed as a spatial map highlighting the relative differences in connectivity of different regions of the brain. Differences between the patient and control group maps were assessed by visual comparison. This approach was taken instead of a statistical comparison because the two groups' fMRI data were acquired using slightly different acquisition parameters, which can lead to subtle but statistically significant differences between functional connectivity maps (Biswal et al., 2010).

In addition to comparing the patient and control groups, we also tested for possible state-dependent functional connectivity differences in the patient group by comparing subjects that were asleep with those that were awake. The values in each subject's connectivity map were first normalised before this comparison, as the degree does not follow a Gaussian distribution (van den Heuvel et al., 2008) as is required for analysis with standard parametric statistics. We used the normalising transformation described in van Albada and Robinson (2007) that has previously been applied for the group analysis of degree maps of functional connectivity (Lohmann et al., 2010). Group comparison was performed using a two-sample t-test, and the map was thresholded to identify significant ($p < 0.05$) clusters based upon a voxel-wise height threshold of $p < 0.001$ (uncorrected) and an extent threshold estimated by Monte Carlo simulation using AlphaSim software (http://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf). It was not possible to test for state-dependent effects in the control group, as those subjects did not have a simultaneous EEG recording to enable sleep-state classification.

A seeded functional connectivity analysis (Biswal et al., 1995) was used to further investigate the functional connectivity of regions identified as showing between-group differences in degree centrality. Seed voxel coordinates were defined by selecting the voxel with maximum degree within each region-of-interest on the group map, and the functional connectivity of these seeds was estimated for each subject using the Pearson's correlation coefficient of voxel time-courses to the seed. Group functional connectivity maps for each seed were estimated by transforming the correlation coefficients into z scores using Fisher's transformation and performing one-sample t-tests. The group connectivity maps were thresholded to identify significant ($p < 0.05$) clusters based upon a voxel-wise height threshold of $p < 0.001$ (uncorrected) and an extent threshold estimated using AlphaSim software.

Results

In all patients GSW-free periods of sufficient duration for the resting-state functional connectivity analysis were identified during the fMRI scanning. For seven subjects a single GSW-free epoch could be identified, whereas four subjects required two separate epochs to be concatenated to provide sufficient data for analysis. Five patients were awake, four were asleep, and two had a mixture of wakefulness and sleep during the selected analysis epochs.

The CAE patients and controls groups showed marked differences in functional connectivity (Fig. 1). The connectivity map for the control group showed high numbers of connections in the thalamus and basal ganglia. In contrast, the average CAE map showed the greatest number of functional connections in the cortex whilst sub-cortical structures had relatively fewer connections.

There were no clear differences between functional connectivity measured in patients who were asleep ($n = 4$) and those who were awake ($n = 5$) (Fig. 2). These maps appeared similar to the connectivity measured across the entire patient group (Fig. 1) and statistical comparison found no significant differences ($p < 0.05$) between the two different states. The numbers in both groups were small, however, so subtle between-group differences may possibly exist that were unable to be detected with the available data.

Functional connectivity was measured seeded from the thalamus and medial occipital cortex, based upon the group differences observed in these regions. The results of seeding from the thalamus (MNI coordinate: −12, −19, 4) (Fig. 3) revealed widespread functional connectivity throughout the brain in the control group, including the basal ganglia, cortex, cerebellum and brainstem. The patient group showed a similar pattern of thalamic functional connectivity, but diminished in both the spatial extent and magnitude of the correlation. The analysis of the medial occipital seed

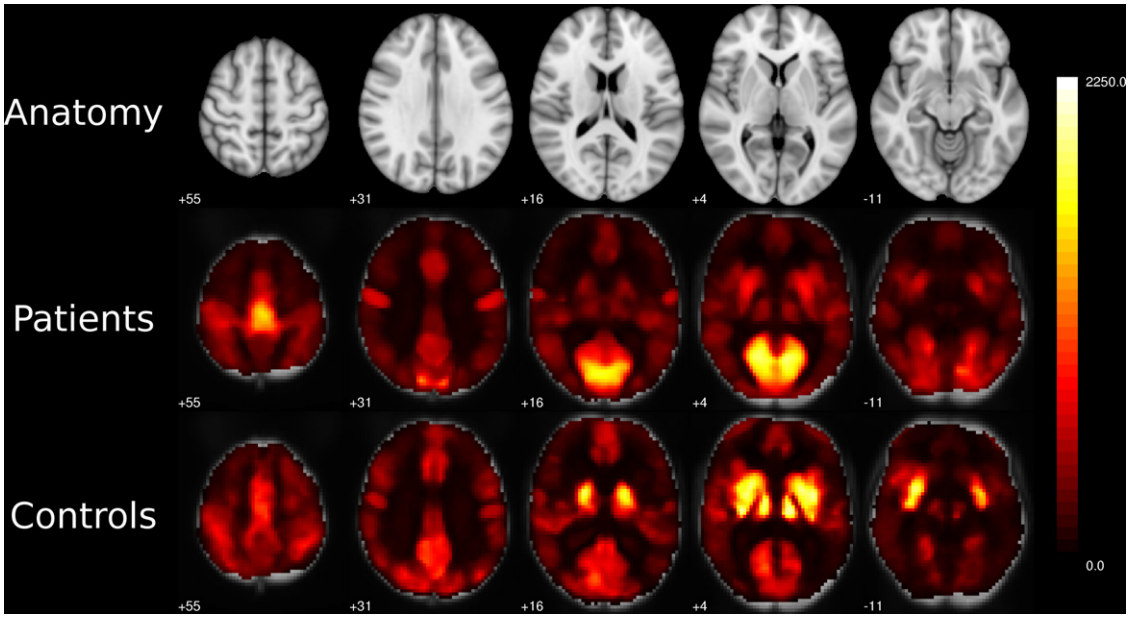

Figure 1 Maps of the functional connectivity degree in the patient and control groups, showing a count of the number of functional connections ($r > 0.6$) at each voxel. Hotter colours represent regions with greater numbers of functional connections. In comparison to the healthy control group, the CAE patients show reduced numbers of functional connections in the sub-cortex — particularly the thalamus and basal ganglia — and increased functional connections in the cortex — including the medial occipital cortex. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

(MNI coordinate: −9, −67, 7), on the other hand, suggested a notably different pattern of functional connectivity between the two groups (Fig. 4). The CAE patients showed greater functional connectivity locally within the occipital cortex than the controls, and included further connectivity to areas of primary cortex. The control group, in contrast, showed functional connectivity to regions of association

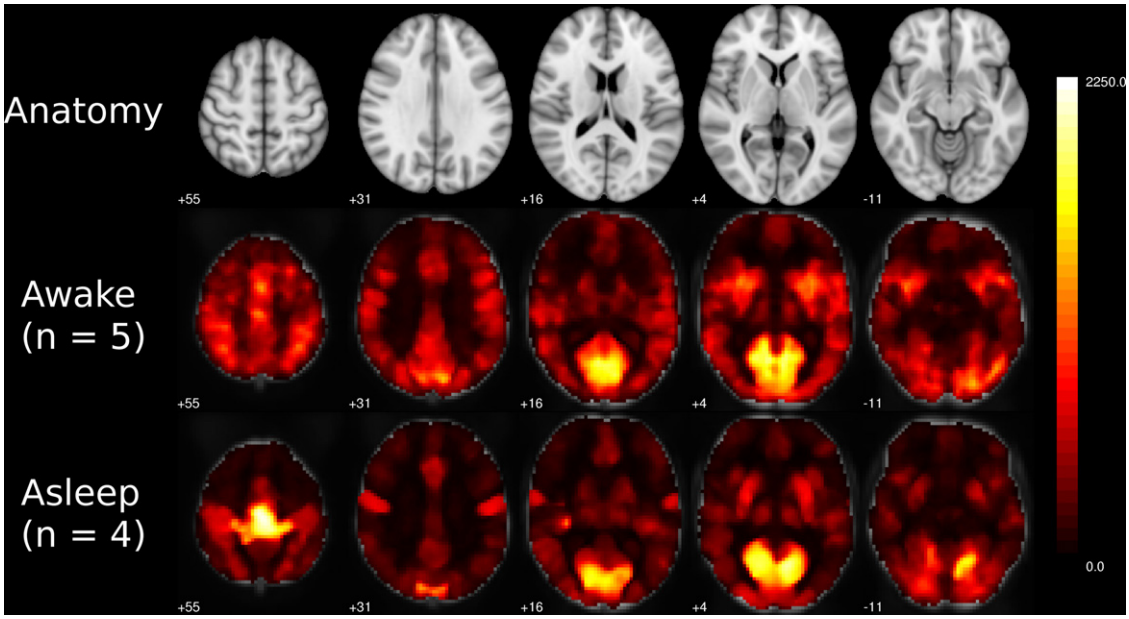

Figure 2 Maps of the functional connectivity degree in patient sub-groups that were asleep ($n = 4$) and awake ($n = 5$) during the GSW-free analysis epoch. The maps show a count of the number of functional connections ($r > 0.6$) at each voxel, with hotter colours representing regions with greater numbers of functional connections. The maps for both groups show a similar pattern of greater numbers of functional connections in the cortex than the sub-cortex, and statistical comparison found no significant differences between the groups ($p < 0.05$, corrected for multiple comparisons). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

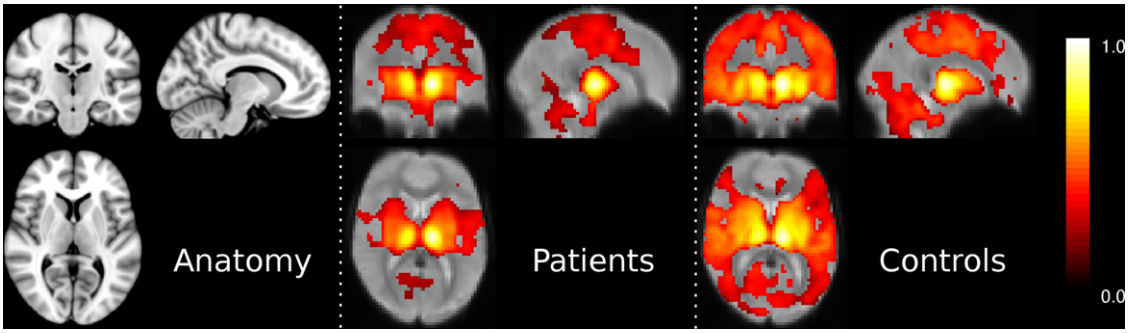

Figure 3 Maps of functional connectivity seeded from the left thalamus (−12, −19, 4) in the patient and control groups. Significant clusters are shown ($p < 0.05$, corrected for multiple comparisons) with the colour indicating the mean r value. The control group shows a more extensive and stronger (i.e. greater r values) pattern of thalamic functional connectivity in comparison to the CAE patient group. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

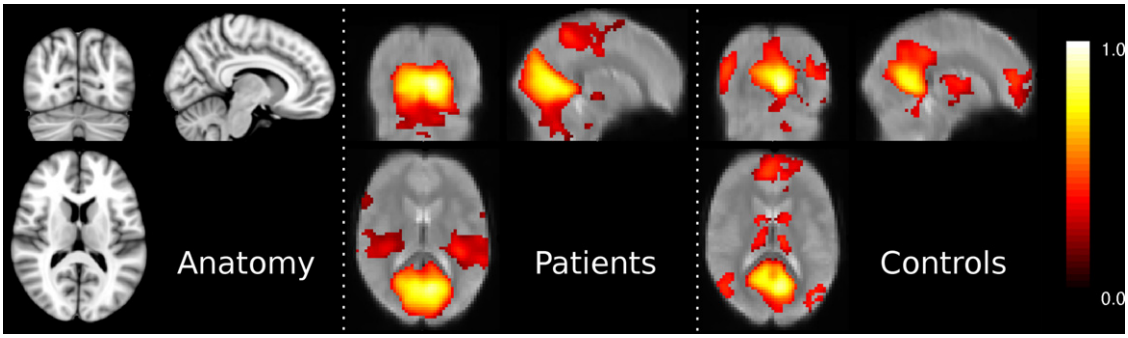

Figure 4 Maps of functional connectivity seeded from the left medial occipital cortex (−9, −67, 7) in the patient and control groups. Significant clusters are shown ($p < 0.05$, corrected for multiple comparisons), with the colour indicating the mean r value. The patient group shows greater functional connectivity locally within the occipital cortex in comparison to the healthy controls. There are also marked differences in functional connectivity to other regions of the brain: the CAE patients predominantly show connectivity to areas of primary cortex, whereas the controls show functional connectivity to regions of association cortex (the ''default-mode'' network), the thalamus and caudate. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

cortex (the ''default-mode'' network), the thalamus and caudate.

Discussion

In this study we measured resting-state functional connectivity in children with CAE, studied off medication. We found differences in sub-cortical and cortical functional connectivity in CAE as compared to healthy controls. The patients had decreased connectivity in the thalamus and basal ganglia and increased connectivity in the medial occipital cortex. The CAE patients had stronger connectivity between medial occipital cortex and primary cortical areas. These connectivity differences are likely to have a functional significance, as resting-state functional connectivity is correlated with task performance, cognitive abilities, and neurological and psychiatric diseases (Fox and Raichle, 2007). Functional connectivity mapping of the thalamus has also been shown to have good correspondence with known anatomical connections (Zhang et al., 2008, 2010).

A number of other recent studies have also reported altered functional connectivity in absence epilepsy patients (Luo et al., 2010; Bai et al., 2011; Killory et al., 2011). These studies have reported functional connectivity decreases (Luo et al., 2010; Killory et al., 2011) and increases (Bai et al., 2011) within specific functional networks in these patients. A single study has found no clear differences in the functional connectivity of ''GSW network'' regions in GGE patients compared with healthy controls (Moeller et al., 2011); however that study was of a mixed cohort of adults with a range of GGE syndromes and medications. These reports provide growing evidence of inter-ictal functional connectivity disturbances in patients with absence epilepsy, although the extent of functional connectivity disruption beyond those specific networks remains unclear.

In this study we investigated only group differences that were clearly evident upon visual inspection of the group maps. This approach was taken because the two groups' data in this study were acquired using slightly different acquisition parameters. Functional connectivity maps estimated using data from different scanners and image acquisitions appear very similar with no marked qualitative differences (Biswal et al., 2010), although statistical comparison may reveal subtle but statistically significant differences due to different scanning parameters (Biswal et al., 2010). For

this reason, the differences identified between the patient and control groups in this study were based upon visual inspection rather than a direct statistical comparison. A consequence of our analysis approach is that subtle effects may possibly have been missed, and future studies may detect even further differences between the two groups.

Functional connectivity between the thalamus and the rest of the brain was reduced in CAE patients (Figs. 1 and 3), suggesting a fundamental change in the interaction between thalamus and cortex. The thalamus has long been known to have a functional role in the generation of GSW (Blumenfeld, 2005), and these findings provide evidence that thalamic function is also abnormal in the ''baseline'' state. This observation of impaired thalamic function complements other evidence of structural and metabolic abnormalities in the thalami of patients with GGE, including reduced grey matter volumes (Chan et al., 2006) and reduced ratios of N-acetylaspartate to creatine (NAA/Cr) regardless of the amount of GSW activity (Bernasconi et al., 2003). Thalamic dysfunction may contribute to the diffuse cognitive deficits in these patients, which include specific memory and attentional functions (Pavone et al., 2001; Henkin et al., 2005), as the thalamus plays a crucial role in networks for memory and attention (Van der Werf et al., 2003).

Changes in arousal and sleep are associated with changes in the mode of thalamic firing, and it is therefore possible that thalamic functional connectivity measurements may also change with these different brain states. To address the possibility that the group differences observed in this study were a result of different sleep states, we sub-divided the patient group based upon sleep assessment from the simultaneous EEG recordings. We found no major differences in functional connectivity between patients sleeping and awake (Fig. 2), which suggests that the marked functional connectivity differences observed between patients and controls are unlikely to be the result of state differences between the two groups.

Connectivity of the medial occipital cortex was increased in CAE patients compared to controls (Fig. 1) and the seeded connectivity analysis showed a striking difference in the pattern of functionally connected structures (Fig. 4). The patients showed mostly functional connectivity to primary visual, auditory and sensorimotor cortical regions. The controls, in contrast, showed functional connectivity between the medial occipital cortex and the thalamus, caudate and ''default-mode'' cortical regions — in other words, the ''GSW network'' that has been shown to activate and deactivate at the time of GSW discharges (Archer et al., 2003; Gotman et al., 2005; Hamandi et al., 2006; Moeller et al., 2008; Carney et al., 2010; Bai et al., 2010). This finding suggests a fundamental change in network connectivity of the medial occipital region. It is not clear whether this represents a primary pathophysiological mechanism or a secondary response of the brain to seizures. The increase in connectivity involving primary cortical regions in patients might reflect increased excitability of primary cortex as seen in the motor cortex of GGE patients using TMS methods (Badawy et al., 2007).

The observation of functional connectivity between the occipital cortex and the ''GSW network'' in healthy control subjects suggests that this might be a normal brain network that is connected with the occipital cortex. This raises the possibility that this area of occipital cortex could ''drive'' this network in pathological circumstances. Although not consistently included as part of the ''core'' GSW network, it is not uncommon in our experience for EEG—fMRI analyses to detect BOLD signal increases in the occipital cortex associated with absence seizures and GSW (unpublished observations), and this has also been reported by others (Bai et al., 2010). Bai et al. (2010) found occipital activation preceded the onset of GSW, and emphasised that the time-course of BOLD changes in this region was not well modelled by a standard haemodynamic response function (HRF), which could explain why occipital activations are often not detected by typical analyses using the standard HRF. Taken together with our current findings, this suggests that the occipital cortex may play an important role in absence seizure generation that warrants further investigation.

In summary, our observation of altered thalamic and cortical functional connectivity in a resting-state free from GSW activity suggests that sub-cortical and cortical functional networks in patients with absence epilepsy have changes that persist beyond the epileptiform events themselves. Although animal models of absence seizures also identify both the cortex and thalamus as crucially involved in GSW generation (Snead, 1995), cortico-thalamic neurons in the somatosensory cortex are thought to be the actual initiators of pathological oscillations within this circuit (Pinault and O'Brien, 2005; Meeren et al., 2002). Our human data, showing functional connectivity changes in both the thalamus and cortex, provide evidence that the pathophysiology of CAE is likely to include dysfunction in both these regions.

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