Resting-state functional connectivity of the thalamus is reduced in absence epilepsy

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Introduction: Genetic generalised epilepsy (GGE) is characterised by episodic brain dysfunction involving widespread hypersynchronous activity appearing as generalised spike wave (GSW) discharges on the EEG. The network of brain regions that are active at the time of these events have been defined using EEG-fMRI [1,2,3,4,5,6]. In addition to these paroxysmal events, GGE patients also show increased cortical excitability [7] and mild ongoing cognitive impairments [8,9], which suggests 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. In this study we hypothesised that functional connectivity would be altered in GGE, due to the presumed disturbance in network activity and function in these patients. To test this hypothesis, we acquired resting-state fMRI in a cohort of patients with untreated childhood absence epilepsy (CAE) and measured functional connectivity using a whole-brain voxel-wise analysis [10]. Simultaneous EEG recordings were used to identify baseline periods for analysis, from GSW-free activity, to avoid transient inter-regional correlations during generalised discharges that might spuriously be interpreted as functional connectivity. We performed a group comparison with healthy controls in order to identify regions of altered functional connectivity.

Methods: CAE patients were recruited using the following selection criteria: onset of absence seizures before age ten; absence as exclusive seizure type at time of study; not currently treated; normal background on routine EEG; 3–5.5 Hz GSW during absence; normal early developmental milestones; and normal structural imaging. Eleven patients (5 male) meeting these criteria were recruited. The patients were aged from 5 to 14 years (mean: 8.7; standard deviation: 2.62). Eleven healthy control subjects (7 male) were retrospectively selected from a database of subjects who have undergone resting-state fMRI scanning. The controls were selected to provide as close an age distribution to the patient group as possible, and were aged from 7 to 12 years (mean: 8.91; standard deviation 1.16).

The fMRI images were acquired on a 3 tesla GE Sigma LX scanner using a BOLD-weighted 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 different scanning parameters. The patient scanning parameters were: 40 slices, 3.2mm thick (+0.2mm gap); TR=3200ms; TE=40ms; FOV = 22cm; matrix = 64x64; and the control scanning parameters were: 25 slices, 4mm thick (+1mm gap); TR = 3000ms; TE = 40ms; FOV = 24cm; matrix = 128x128. Simultaneous EEG recordings were also obtained during the patients’ scanning session in order to detect bursts of GSW. For each subject one-hundred whole-brain volumes were used for functional connectivity analysis. For the patients we selected periods of “baseline” brain activity during which no GSW were detected. We also required that each period of baseline be proceeded by a minimum of thirty seconds and followed by a minimum of ten seconds of GSW-free EEG. If a continuous GSW-free period could not be identified, we created a composite dataset by concatenating shorter periods [12] – with the requirement that each such sub-section was of a minimum of two minutes duration.

The fMRI data were pre-processed with SPM8 software [www.fil.ion.ucl.ac.uk/spm]. The pre-processing steps were: slice-timing correction, realignment to correct for subject motion, spatial normalisation, re-sampling to 3mm isotropic voxels, and spatial smoothing with a Gaussian kernel (FWHM = 8mm). Physiological noise components were modelled based upon the realignment parameters and average signals within white matter and cerebrospinal fluid (CSF) compartments [11] and were estimated at each voxel using linear regression and subtracted from the data.

Functional connectivity was assessed by comparing all pairs of within-brain voxels. The voxel time-courses were band-pass filtered (0.01–0.1 Hz) [13] and the existence of a connection was inferred if the Pearson’s correlation coefficient between two voxels was greater than 0.6. A map of global connectivity for each subject was then formed by counting the number of functional connections (the “degree”) at each voxel [10]. Statistical comparison between the two groups was performed using SPM8. It has been suggested that the degree distribution of functional connectivity follows a power-law [10], so we applied a transformation to each subject’s raw map to ensure a normal distribution [14] in order to allow for parametric testing.

Results: The two groups showed marked differences in functional connectivity (Figure 1). The averaged 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. Statistical comparison revealed significant group differences (p < 0.05; corrected for multiple comparisons) bilaterally in the thalamus, basal ganglia, precuneus and postcentral gyrus.

Discussion: Altered connectivity in the precuneus is an interesting finding, as this region of cortex is commonly observed to deactivate at the time of GSW [1,2,3,4,5,6]. It has been suggested that this deactivation may occur secondarily to GSW and simply reflect the attenuation of a network that is actively engaged during the resting-state [2,15], although evidence for a more active role is provided by recent reports showing that the onset of activity within the precuneus may precede GSW [5,6]. Our findings of altered functional connectivity in this region support the notion that “deactivation” of the precuneus during GSW is not simply an interruption to an otherwise normal resting-state network.

The marked reduction in functional connectivity of the sub-cortex is a particularly striking finding. The thalamus has long been known to have a functional role in the generation of GSW [16]. Our findings now also provide evidence of altered thalamic function in the baseline state. This complements other evidence of structural and metabolic thalamic abnormalities in GGE, including reduced grey matter volumes [17] and reduced ratios of N-acetylaspartate to creatine (NAA/Cr) regardless of the amount of GSW activity [18].

The functional consequences of reduced thalamic functional connectivity are not clear. It is possible that a reduction in thalamic mediated cortical inhibition contributes to the increased resting-state cortical excitability observed in untreated IGE patients [7] and hence thalamic functional connectivity is reduced at rest. This is supported by a report that deep brain stimulation of the thalamus can reduce cortical excitability in epilepsy [19]. The thalamus also plays a crucial role in networks for memory and attention [20], so reduced thalamic functional connectivity may explain some of the diffuse cognitive deficits that are associated with CAE [8,9].

In summary, our observation of functional connectivity abnormalities in a resting-state free from GSW activity suggests an enduring change in sub-cortical and cortical functional networks as part of the underlying pathophysiology of CAE.


Figure 1: Differences in functional connectivity between untreated CAE patients and healthy controls. The top two rows show the average connectivity measured in the two groups, with hotter colours indicating greater connectivity. The bottom rows show a t-statistic map highlighting areas of significant (p < 0.05 corrected for multiple comparisons) connectivity differences.