Investigating the role of interictal activity during a natural stimulus presentation in children with epilepsy

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Introduction: Patients with focal epilepsy often have cognitive deficits, but the role of epileptic discharges and seizures in modifying cognition is not well understood. Resting state (RS) fMRI studies in epilepsy patients have shown network abnormalities. In particular, abnormalities have been frequently reported in the so-called 'default mode' network (DMN) which is most active during rest[1-2]. However, the underlying mechanisms that lead to these abnormalities, and in particular the role of ongoing interictal epileptiform discharges (IEDs), and the relevance of the RS networks for cognition are unclear. We therefore decided to study alterations in network properties due to IEDs both during 'rest' and during a 'natural stimulus' video task requiring low level attention.

Methods: We collected simultaneous EEG-fMRI data at 1.5T using an MRI compatible EEG system. Subjects included 13 pre-surgical drug-resistant patients with mixed localisation and 11 age-matched controls, all between the ages of 9-18. fMRI data was obtained at 3.3x3x4mm resolution, TR=2160ms, TE=30ms, and 300 volumes. Four sessions of 10m48s duration were recorded: two sessions of rest, and two sessions of task. The task presented was a video condition watching a cartoon and a condition presenting a screen with the words 'please wait'. Retrospective motion correction was applied using FIACH (Functional Image Artefact Correction Heuristic- methodological details submitted in abstract) [3]. FIACH is a biophysical model of motion correction that employs a two-step procedure for motion correction. The first step identifies regions of high temporal instability using the expectation-maximisation algorithm and extracts the first 6 principal components from these areas. These components are included at the regression stage of the analysis as effects of no interest. The second step identifies large amplitude signal changes due to through-plane movement and corrects them with a spline filter. EEG was corrected for in-scanner artefacts and interictal epileptic events (IEDs) visually identified by an expert clinician. Following standard pre-processing in SPM8 (www.fil.ion.ucl.ac.uk), each subjects' 4 sessions were entered into a general linear model containing the task, IEDs and effects of no interest. A general linear model (GLM) analysis was performed looking at blocks of task (video and 'please wait' conditions) which were entered as a regressor. In each individual a positive and negative T-contrast was used to show regions with greater activity in each condition. Group effects were subsequently tested between the groups in a second level analysis using these maps. The functional connectivity analysis was performed using conn (http://www.nitrc.org/projects/conn). Seed to voxel analysis used brain regions generated by the GLM group level differences to reveal network differences between patients and controls. We used a statistical threshold of p<0.001 with voxel extend k=20.

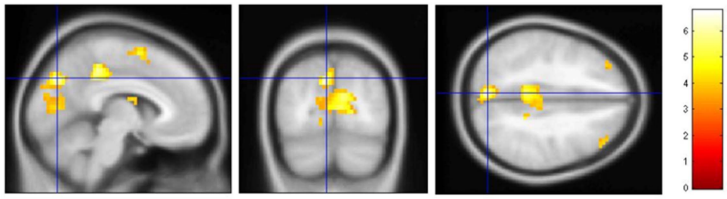

Figure 1: A group level analysis of **controls > patients** based on the contrast for **'Please Wait' > 'Video'** using a one-sampled t-test threshold at p<0.001 and extent voxel threshold at 20.

Results: We found significant group level differences in the response to the low level task between patients and controls in the dorsal anterior cingulate, frontal poles, posterior cingulate, and precuneus regions, which are usually associated with the salience and default mode networks (DMN) respectively (see Figure 1).

We explored if there were differences in functional connectivity within the salience (see Figure 2) and DMN networks (see Figure 3). We found that there was stronger intra-network connectivity in controls compared to patients. These differences became significantly smaller when controlling for IEDs (see Table 1-2). This result shows that brain networks that should be connected during a task block are perturbed by IEDs but their overall response to the task is not. Accounting for IEDs is important to interpret functional connectivity results in epilepsy.

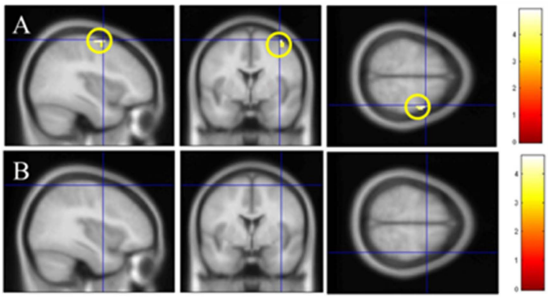

Figure 2: Seeded region Dorsal Anterior Cingulate from Salience Network node. A) Not controlling for interictal activity B) Controlling for interictal activity in the model.

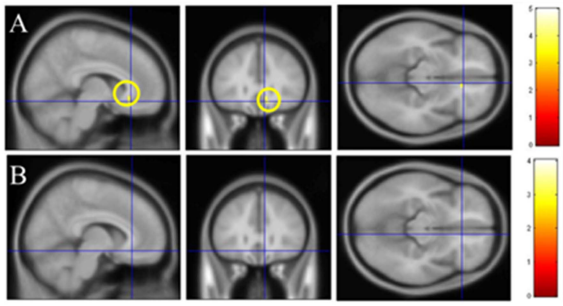

Figure 3: Seeded region Precuneus from DMN. A) Not controlling for interictal activity B) Controlling for interictal activity in the model.

IED	L/R	Label	X, Y, Z	Cluster Size
Not	L	Dorsal Frontal Cortex	-32, 40, 36	157
Controlled	R	Dorsal Frontal Cortex	48, 46, 20	93
	R	Premotor Cortex	40, -4, 62	56
	R	Premotor Cortex	58, 8, 4	22
Controlled	L	Dorsal Frontal Cortex	-32, 40, 36	112
	R	Dorsal Frontal Cortex	46, 50, 16	24

Table 1: Seed DACC with and without interictal activity controlled for controls>patients with voxel threshold p<0.001 cluster threshold k=20.

IED	L/R	Label	X, Y, Z	Cluster Size
Not Controlled	R	Ventral Anterior Cingulate Cortex	12, 28, -12	20
Controlled	N/A	N/A	N/A	N/A

Table 2: Seed precuneus with and without interictal activity controlled for controls>patients with voxel threshold p<0.001 cluster threshold k=20.

Discussion: We have shown the effect of epilepsy on specific networks during a low level attentional task despite a heterogeneous group of focal epilepsy patients. Interictal activity seems to be a major component of connectivity differences in patients versus controls, and should therefore be accounted for in the future.

References: **1.** Liao W, Zhang Z, Pan Z, et al. Default mode network abnormalities in mesial temporal lobe epilepsy: A study combining fMRI and DTI. Human Brain Mapping. 2011;32(6):888-895. **2.** Widjaja E, Zamyadi M, Raybaud C, et al. Abnormal Functional Network Connectivity among Rest-State Networks in Children with Frontal Lobe Epilepsy. AJNR. 2013; 34(12):2386-2392. **3.** Tierney T, Croft L, Centeno M, et al. A Biophysical Model for Automatic Retrospective Motion Correction in fMRI. Poster presented at the Motion Correction in MRI Conference, 2014. Tromso, Norway.