

**Full Title:** *Simultaneous intracranial EEG-fMRI shows inter-modality correlation in time-resolved connectivity within normal areas but not within epileptic regions*

**Authors:** Ben Ridley<sup>a,b</sup>, Jonathan Wirsich<sup>a,b,c</sup>, Gaelle Bettus<sup>a,b,c</sup>, Roman Rodionov<sup>d,e</sup>, Teresa Murta<sup>d,f</sup>, Umair Chaudhary<sup>d,e</sup>, David Carmichael<sup>g</sup>, Rachel Thornton<sup>d,e</sup>, Serge Vulliemoz<sup>d,e,h</sup>, Andrew McEvoy<sup>d,e,i</sup>, Fabrice Wendling<sup>j,k</sup>, Fabrice Bartolomei<sup>c,l</sup>, Jean-Philippe Ranjeva<sup>a,b</sup>, Louis Lemieux<sup>d,e</sup>, Maxime Guye<sup>a,b</sup>

**Affiliations:** <sup>a</sup> Aix-Marseille Univ, CNRS, CRMBM UMR 7339, Marseille, France <sup>b</sup> APHM, Hôpitaux de la Timone, CEMEREM, Marseille, France <sup>c</sup> Aix Marseille Univ, Inserm, INS, Institut de Neurosciences des Systèmes, Marseille, France <sup>d</sup>Institute of Neurology, University College London (UCL), London, UK, WC1N 3BG. <sup>e</sup>MRI Unit, Epilepsy Society, Buckinghamshire, UK, SL9 0RJ. <sup>f</sup>Institute for Systems and Robotics and Department of Bioengineering, Instituto Superior Técnico, Universidade de Lisboa, Lisboa, Portugal. <sup>g</sup>Institute of Child Health, UCL, London, UK, WC1E 6BT. <sup>h</sup>EEG and Epilepsy Unit, Neurology Clinic, University Hospitals and Faculty of Medicine of Geneva, Switzerland, CH-1211. <sup>i</sup>Department of Neurosurgery, National Hospital for Neurology and Neurosurgery, London, UK, WC1N 3BG. <sup>j</sup>INSERM, U1099, Rennes, F-35000, France. <sup>k</sup>Université de Rennes 1, LTSI, F-35000, France. <sup>l</sup>APHM, Hôpitaux de la Timone, Service de Neurophysiologie Clinique, Marseille, France

**Author Email:** ben.ridley@univ-amu.fr; jonathan.wirsich@univ-amu.fr; gaelle.bgimeno@gmail.com; r.rodionov@ucl.ac.uk; teresa.murta.11@ucl.ac.uk; umair.chaudhary@ucl.ac.uk; d.carmichael@ucl.ac.uk; Rachel.Thornton@gosh.nhs.uk; Serge.Vulliemoz@hcuge.ch; a.mcevoy@ucl.ac.uk; fabrice.wendling@univ-rennes1.fr; fabrice.bartolomei@ap-hm.fr; jean-phillipe.ranjeva@univ-amu.fr; louis.lemieux@ucl.ac.uk; maxime.guye@ap-hm.fr

**Corresponding Author:** Ben Ridley. **Address:** CEMEREM, 264 rue Saint-Pierre, Marseille, 13385, France. **Email:** ben.ridley@univ-amu.fr **Tel:** +33 (0) 4913388467 **Fax :** +33 (0) 491388461

**Compliance with Ethical Standards:** The authors declare no competing financial interests. The authors obtained written informed consent from all patients, in compliance with the ethical requirements of the Declaration of Helsinki and the Joint Research Ethics Committee of the NHNN (UCLH NHS Foundation Trust) and UCL Institute of Neurology.

**Acknowledgements:** Data for this was acquired at UCLH/UCL who received a proportion of funding from the Department of Health's NIHR Biomedical Research Centres funding scheme. Processing and analysis were undertaken at CRMBM/CEMEREM. This work was also supported with funds from the Swiss National Science Foundation (141165 and 140332, SPUM Epilepsy).

38

39

40 **Abstract**

41 For the first time in research in humans, we used simultaneous icEEG-fMRI to examine the link  
42 between connectivity in haemodynamic signals during the resting-state (rs) and connectivity derived  
43 from electrophysiological activity in terms of the inter-modal connectivity correlation (IMCC). We  
44 quantified IMCC in 9 patients with drug-resistant epilepsy i) within brain networks in ‘healthy’ non-  
45 involved cortical zones (NIZ) and ii) within brain networks involved in generating seizures and  
46 interictal spikes (IZ1) or solely spikes (IZ2). Functional connectivity ( $h^2$ ) estimates for 10 minutes of  
47 resting-state data were obtained between each pair of electrodes within each clinical zone for both  
48 icEEG and fMRI. A sliding window approach allowed us to quantify the variability over time of  $h^2$   
49 ( $vh^2$ ) as an indicator of connectivity dynamics. We observe significant positive IMCC for  $h^2$  and  $vh^2$ ,  
50 for multiple bands in the NIZ only, with the strongest effect in the lower icEEG frequencies.  
51 Similarly, intra-modal  $h^2$  and  $vh^2$  were found to be differently modified as a function of different  
52 epileptic processes: compared to NIZ,  $h^2_{\text{BOLD}}$  was higher in IZ1, but lower in IZ2, while  $h^2_{\text{icEEG}}$   
53 showed the inverse pattern. This corroborates previous observations of inter-modal connectivity  
54 discrepancies in pathological cortices, while providing the first direct invasive and simultaneous  
55 comparison in humans. We also studied time-resolved FC variability multimodally for the first time,  
56 finding that IZ1 shows both elevated internal  $h^2_{\text{BOLD}}$  and less rich dynamical variability, suggesting  
57 that its chronic role in epileptogenesis may be linked to greater homogeneity in self-sustaining  
58 pathological oscillatory states.

59

60

61

62 **Keywords:** connectivity; multimodal imaging; resting-state; focal epilepsy; dynamic connectivity

63

64 **Abbreviations:**

65 ECoG – Electrocorticography

66 FC – Functional Connectivity

67 FLE – Frontal Lobe Epilepsy

68 IED – Interictal Epileptic Discharges

69 icEEG – Intracranial Electroencephalography

70 ICN – Intrinsic Connectivity Network

71 IZ – Irritative Zone

72 NIZ – Non-involved Zone

73 TLE – Temporal Lobe Epilepsy

74 SEEG – stereo-electroencephalography

75

## 76 1. INTRODUCTION

77 The advent of multimodal approaches for investigating brain activity, and the range of  
78 methods for quantifying oscillatory phenomena in the resting-state, provide both the potential for  
79 novel insight and novel challenges. Interpretation of scalp EEG-fMRI data is complicated by the fact  
80 that scalp EEG is affected by conductively inhomogeneous head tissue, and is limited in relation to  
81 buried structures (Carmichael, Vulliemoz et al. 2012). Pre-surgical evaluation in drug-resistant  
82 epilepsies commonly involves implantation of electrodes (Rosenow and Luders 2001). Thus, this  
83 population proffers a unique opportunity to investigate the relationship between haemodynamic and  
84 electrophysiological phenomena in both ‘healthy’ regions not involved in epileptic activity and  
85 regions subject to paroxysmal pathology, via an invasive method not normally permissible in human  
86 samples.

87 Intracranial EEG (icEEG) is the gold standard for categorising cortices in terms of  
88 epileptogenicity and involves the implantation of electrodes in the form of subdural grids or strips for  
89 electrocorticography (ECoG) and/or stereo-electroencephalography (SEEG) via depth electrodes  
90 (Rosenow and Lüders 2001). For example, icEEG can be used to define and categorise the set of brain  
91 regions involved in the generation of paroxysmal interictal epileptiform discharges (IEDs), called the  
92 Irritative Zone (IZ) (Chauvel 2001; Palmini 2006; Bartolomei et al. 2016). The IZ can be further sub-  
93 divided into the IZ1, involved in generating seizure (ictal) activity as well as IEDs, and the IZ2,  
94 exclusively involved in the generation of IEDs.

95 In recent years, conventional functional brain-mapping has been complemented by resting-  
96 state functional connectivity (rsFC) – the analysis of statistical interdependencies in the spontaneous  
97 time courses of activity between remote regions – as a means of understanding the role of networks in  
98 distributed function in normal and pathological brains (Guye et al. 2008; Sporns 2014; Raichle 2015).  
99 Functional connectivity analyses in controls have revealed macro-scale intrinsic connectivity  
100 networks (ICNs) (Smith et al. 2009). In epilepsy, rsFC analyses have been applied to both such  
101 anatomically-defined ICNs, in addition to clinically-determined networks that vary anatomically from  
102 patient to patient but are unified in terms of the disease processes they manifest, such as IZ1 and IZ2  
103 (Guye et al. 2010; Laufs 2012; Centeno and Carmichael 2014). The hope is that FC analyses in the  
104 interictal resting-state, with their limited demands on patients and without the need to wait for  
105 unpredictable ictal and inter-ictal activity, can facilitate the understanding of epilepsy in the both the  
106 lab and clinic. While substantial study has been made of changes to ICNs, less has been done to  
107 understand clinically-defined epileptic networks via the rsFC paradigm. Often taking advantage of the  
108 spatial resolution and whole brain coverage of fMRI, such studies have indicated distributed changes  
109 including both augmented and impaired connectivity with links to pathological and potentially  
110 compensatory processes in epilepsy (Bettus et al. 2009; Bettus et al. 2010; Zhang et al. 2010; Centeno

111 and Carmichael 2014; Holmes et al. 2014; Ridley et al. 2015). While region of interest (ROI)  
112 selection in such studies may be motivated by an understanding of the likely candidates for  
113 involvement in epileptogenesis [cf. Bettus et al., 2009], they may still fail to account for individual  
114 variation in the actual location and extent of pathological activity. A small number of studies have  
115 taken advantage of the greater specificity of icEEG relative to *a priori* regions of interest when  
116 parcellating cortices into irritative and physiological/non-involved zones (NIZ) to explore functional  
117 connectivity specifically as a function of involvement in different epileptic processes in the interictal  
118 resting-state (Bartolomei et al., 2013; Bartolomei et al., 2013; Bettus et al., 2008; Schevon et al.,  
119 2007; Warren et al., 2010). Such studies indicate increased functional connectivity as measured by  
120 icEEG (icEEG-FC) in regions involved in interictal epileptiform activity in comparison to spared  
121 cortices.

122 To our knowledge, Bettus et al. (2011) is the only study to have used the specificity of the  
123 icEEG gold standard in parallel with BOLD-derived FC estimates from the same location, within the  
124 same individuals. These authors showed an apparent inter-modality discrepancy: higher FC as  
125 revealed by icEEG and lower FC as measured by BOLD in electrophysiologically abnormal regions.  
126 However, since both modalities were not acquired simultaneously, confounding inter-session effects  
127 cannot be ruled out as an explanation. For example, impacts arising from the time of day of  
128 acquisition, emotional/mental state (including sleep) and consumption of pharmacological agents such  
129 as caffeine or nicotine have been shown to effect connectivity (Duncan and Northoff 2013).  
130 Furthermore, variation in connectivity over time has recently become a target of interest as possibly  
131 physiological signal reflecting the dynamic formation and integration of functional and dysfunctional  
132 assemblies (Tagliazucchi and Laufs 2015). Epilepsy is recognized as involving modifications on  
133 multiple time scales, not only chronic modifications to structural and functional networks (Spencer  
134 2002; Laufs 2012; Bartolomei et al. 2013b). Like seizures, IEDs may impact connectivity  
135 intermittently and on timescales smaller than the several minutes generally averaged over in ‘static’  
136 functional connectivity estimates (Centeno and Carmichael 2014; Lopes et al. 2014). While the  
137 biophysical underpinnings remain unclear, variance in resting BOLD signal oscillations is spatially  
138 organized (Kaneoke et al. 2012), and the modulation of its standard deviation between cognitive states  
139 is modulated by age and processing speed (Garrett et al. 2013), suggesting that it is a biologically  
140 informative feature and more than mere noise (Garrett et al. 2010) . Similarly, the variation of FC  
141 induced by non-stationarities during the resting-state/interictal period is starting to be investigated via  
142 sliding window analyses in the context of epilepsy (Laufs et al. 2014; Douw et al. 2015; Nedic et al.  
143 2015). These indicate a modification in the variability of FC in regions with plausible *a priori*  
144 relationships to seizure generation and semiology. The advent of simultaneous icEEG-fMRI  
145 (Carmichael et al. 2010; Vulliemoz et al. 2011; Carmichael et al. 2012) offers the possibility of

146 verifying this 1) within invasively *confirmed* epileptic regions and 2) ensuring the equal incidence of  
1 147 non-stationarities via the only means possible: simultaneous acquisition.

3 148 Here we take advantage of simultaneously acquired icEEG-fMRI data to study functional  
4  
5 149 connectivity with the benefit of both greater specificity of separation of cortices in terms of disease  
6  
7 150 process involvement and the exclusion of inter-session effects and differences in non-stationarities.  
8  
9 151 Greater multimodal agreement in the current work would suggest previously observed multimodal  
10  
11 152 discrepancies are due to intersession effects, while the contrary case would implicate ‘genuine’  
12  
13 153 differences in the signals being measured and/or their relationships. Extending this to time-resolved  
14  
15 154 variability in FC, allows us to characterise the range of variability in normal regions, and whether the  
16  
17 155 repertoire of functions states is impacted differentially by chronic exposure to different kinds of  
18  
19 156 epileptic activity. Leveraging simultaneous icEEG-fMRI for the first time in the interictal resting  
20  
21 157 state, we aimed to explore the strength and the multimodal relationships of FC and its variance, both  
22  
23 158 in physiological regions not involved in epileptic processes (NIZ) as well as in diseased regions (IZ).

24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

160 **2. MATERIALS AND METHODS**

161 **2.1. Subjects**

162 Nine (three female, mean age  $30.4\text{rs}\pm 4.5\text{yrs}$ , range 24-38yrs) subjects with drug-resistant  
163 epilepsy undergoing presurgical evaluation for resective surgery gave their informed consent to take  
164 part in this study, which was approved by the Joint Research Ethics Committee of the National  
165 Hospital for Neurology and Neurosurgery (NHNN, UCLH NHS Foundation Trust) and UCL Institute  
166 of Neurology, London, UK. See **Table 1** for full demographic information. All patients were  
167 recruited, monitored long-term and received simultaneous icEEG-fMRI at the NHNN, Queen Square,  
168 London, UK

169

170 **2.2. Intracranial electrode implantation and categorization**

171 Intracranial electrodes were implanted under general anaesthesia to test clinical hypotheses  
172 about the localization of epileptogenic regions. Following implantation, the patients underwent a CT  
173 scan to permit precise localisation of icEEG electrodes. Patients were then monitored in-clinic for an  
174 extended period to gather information regarding ictal and interictal pathological activity using icEEG.  
175 This information was used to characterize each electrode as belonging to a zone involved by different  
176 epileptic processes.

177 The epileptogenic/primary irritative zone (IZ1), the secondary irritative zone (IZ2), and the  
178 non-involved zone (NIZ) were determined for each patient, following Bettus et al (2011). IZ1 was  
179 defined as the subset of brain regions involved in the generation of seizures which may also exhibited  
180 interictal epileptic discharges (IEDs). IZ2 was defined as those regions only secondarily involved in  
181 seizures and which produce interictal spikes. Finally, NIZ were defined as structures without  
182 epileptiform discharges during clinical monitoring. After this monitoring period, the simultaneous  
183 icEEG-fMRI acquisitions analysed below were obtained within the 24 hours prior to electrode  
184 removal.

185 Grids or strips of electrodes were placed on the cortical surface, or penetrated the brain via  
186 multi-contact depth electrode leads. Grids were 4mm diameter disks with 2.3 mm diameter exposures,  
187 made of 90% platinum, 10% iridium. Depth electrodes were made of platinum and were either 0.9 or  
188 1.1mm in diameter, and 2.3 or 2.4 mm in length. Within a given array, electrodes were spaced at  
189 intervals of 10mm for ECoG/grids/strips and 5mm or 10mm for depth. In situ, and across all arrays  
190 and individual implantation schemes, the mean inter-electrode Euclidean distance was  $44\pm 24\text{mm}$ .  
191 **Figure 1** depicts the position of electrodes and their labelling for each participant. For a detailed  
192 account of the clinical implantation targets and implanted electrodes see **Supporting Information S1**.

193

194

### 195 2.3. Resting-state simultaneous icEEG-fMRI acquisition and pre-processing

196 During 10 minutes of simultaneous icEEG-fMRI acquisition, patients were requested to lie at  
197 rest with their eyes open. MRI data were acquired using a 1.5 T Siemens Avanto scanner (Siemens,  
198 Erlangen, Germany) running software version VB15, with a quadrature head transmit–receive RF coil  
199 using low specific absorption rate (SAR) sequences ( $\leq 0.1$  W/kg head average). The following scans  
200 were performed: 1) localiser, 2) FLASH T1-volume (TR:3s/TE: 40 ms/flip angle:  $90^\circ$ ), 3) a GE-EPI  
201 fMRI resting-state scan (TR: 3s/TE: 78 ms/38 slices/200 volumes,  $3 \times 3 \times 3$  mm voxels). BOLD-FC  
202 data were pre-processed using SPM8 software (UCL Wellcome Trust Centre, London, UK). After  
203 slice-timing correction, images were realigned before spatial normalization (16 non-linear registration  
204  $7 \times 6 \times 7$  basis functions) and smoothing (8 mm). Detrending and filtering (0.01-0.08 Hz) were applied  
205 using the REST SPM8 toolbox. Sources of spurious or regionally non-specific variance related to  
206 physiological artefacts were removed via regression of signals from manually defined ROIs in the  
207 lateral ventricles and deep cerebral white matter using SPM’s ‘Marsbar’ toolbox. Maximum  
208 framewise displacement (mm) in 3 translational and rotational planes (degrees of arc converted to  
209 millimetres of displacement as per Power et al (2012)) did not exceed 1mm in any patient (average  
210 maximum displacement (mm) across patients: x: 0.09, y: 0.13 , z: 0.28, pitch: 0.17, roll: 0.12, yaw:  
211 0.13).

212 Following co-registration of the post-operative CT scan and T2\* images with the T1  
213 (normalized mutual information, SPM8) a 5mm radius spherical ROI was defined for each electrode  
214 contact. Given the cortical surface placement of grid contacts, and the wish to ensure only neural  
215 signals were captured by ROIs, grid-derived spherical ROIs were placed normal to and entirely  
216 submerged under the cortical surface immediately adjacent to the corresponding electrode contact. A  
217 ROI fMRI signal time course was extracted by averaging the pre-processed fMRI over the ROI’s  
218 voxels from T2\* images.

219 icEEG signals from subsets of the implanted electrodes (henceforth called *recording*  
220 *electrodes*) were recorded using an MR-compatible amplifier system (Brain Products, Munich,  
221 Germany) and dedicated recording software (*Brain Vision Recorder*) as described in Vulliemoz et al.  
222 (2011) and Carmichael et al. (2012) during the fMRI scans. Recording electrodes were selected based  
223 on the interpretation of the clinical recordings in order to focus on the channels of greatest scientific  
224 interest given the work involved in connecting the electrodes to the MRI-compatible system and, in  
225 some patients, due to the smaller number of channels available in the MRI-compatible amplifier  
226 compared to the number of implanted electrodes. The EEG recording system (0.5  $\mu$ V amplitude  
227 resolution) - sampling at 5 kHz - was synchronised to the scanner's 20 kHz gradient clock, with  
228 subsequent filtering and down-sampling to 250 Hz. Scanning-related artifacts were removed using  
229 standard implementation of template subtraction and filtering (Allen et al. 2000) in the *Brain Vision*

230 *Analyzer* software (V1.3). Data was analysed after subtracting the common average reference  
 231 (minimum number of electrodes included: 30, P01), and filtered according to several frequency ranges  
 232 of interest: broadband (0.5-100Hz), Delta (0.5-3.4 Hz); Theta (3.4-7.4 Hz); Alpha (7.4-12.4 Hz); Beta  
 233 (12.4-24 Hz); and Gamma (24-100 Hz).

234 While every recording electrode was used to define an ROI, the icEEG and fMRI data were  
 235 subject to visual inspection by experts [GB and FB] and overly noisy and likely artifactual timeseries  
 236 of either modality were excluded from all analyses. Using this approach, 13 leads/ROIs were rejected  
 237 (6 grid electrodes from P03 and one depth from P06 due to icEEG data, and 6 grid electrodes from  
 238 P06 due to BOLD data) and 570 were retained. **Table 2** provides a breakdown of the number of ROIs  
 239 provided for the final analysis by each patient.

## 240 2.4 Functional connectivity analysis

241 A nonlinear measure of covariance,  $h^2$ , was used to estimate functional connectivity between  
 242 every pair of electrodes. See Wendling et al. (2010) for an in depth account of this metric. Briefly,  
 243 dependency between two signals  $X$  and  $Y$  derived from the same modality was quantified using:  
 244

$$245 h^2(\tau) = 1 - \frac{\text{VAR}\left[\frac{Y(t+\tau)}{X(t)}\right]}{\text{VAR}[Y(t+\tau)]}$$

246 With

$$247 \text{VAR}\left[\frac{Y(t+\tau)}{X(t)}\right] \triangleq \arg \min_h \left( E[Y(t+\tau) - h(X(t))]^2 \right)$$

248 where  $h$  is a nonlinear fitting curve which approximates the relationship between  $X$  and  $Y$  and  $t$  is the  
 249 time shift that maximizes the value of the  $h^2$  coefficient.

250 Conceptually,  $h^2$  is a normalized non-linear correlation coefficient which quantifies the  
 251 reduction of variance in  $Y$  when  $X$  is used to predict  $Y$  samples. When  $h^2_{XY}=1$ ,  $Y$  is fully determined by  
 252  $X$ , and  $h^2_{XY}=0$  when no relationship exists between the two signals. While it is known that non-  
 253 linearities can occur in EEG signals especially in epilepsy (Casdagli et al. 1997; van Diessen et al.  
 254 2015), the relative importance of being able to detect linear and non-linear components of  
 255 relationships between signals is a subject of ongoing discussion (Netoff et al. 2004; Wendling et al.  
 256 2010). Note that  $h^2$  is a measure of amplitude/power covariance and indicates the presence and  
 257 strength of relationships (and does not, *per se*, differentiate between ‘correlations’ and  
 258 ‘anticorrelations’), with the advantage of not making any assumptions regarding their nature - linear  
 259 or otherwise (Wendling et al. 2010). Additionally, the use of  $h^2$  allows comparison with our previous  
 260 findings in non-simultaneous recordings (Bettus et al. 2011).



263  $h^2$  values between pairs of electrodes or ROIs were computed over sliding window analyses,  
264 separately for each modality. When computing  $h^2_{icEEG}$  between electrodes a 5s window moving with  
265 0.5s increments was used, while for computing  $h^2_{BOLD}$  between ROIs a 90s window moving with 2s  
266 increments was used. Window size was motivated by the need to be large enough to include  
267 uncorrelated (in time)  $X$ - $Y$  values in order to compute a meaningful correlation, and on the assumption  
268 that 50 uncorrelated couples of  $X$ - $Y$  values are needed for reliably computing the  $h^2$  coefficient.  
269 Taking the auto-correlation function for EEG to be 100ms (Wendling et al. 2001), 50 samples  
270 provides a 5 second window size. 1.8 seconds was taken to be sufficient to include minimal  
271 autocorrelation given evidence that the autocorrelation coefficient of resting-state BOLD oscillations  
272 (TR=3s) in healthy controls drops sharply after one second and reaches zero on the order of two  
273 seconds, and 50 samples yields a 90 second window (Kaneoke et al. 2012).

274 The  $h^2$  values were averaged across windows over the entire scanning period time in order to  
275 get a single estimate of static functional connectivity ( $h^2$ ). Additionally, the variation of  $h^2$  over time  
276 ( $vh^2$ ) was computed as the standard deviation of the  $h^2$  estimates for each window across the entire  
277 run. An estimate of  $h^2$  and  $vh^2$  was obtained for BOLD, and for broadband and five sub-bands for  
278 icEEG signals. A thresholding procedure outlined in **Supporting Information 2** was used to verify  
279 that all pairwise relationships constituted evidence for the existence of a correlation between variables  
280 of interest at the 99% level of confidence.

281 In order to take advantage of a pre-existing module of the AMADEUS software (Wendling et  
282 al. 2010; Wendling 2015) - designed to compute large sets of pairwise  $h^2$  - for our BOLD data and to  
283 ensure equivalency of processing it was necessary to resample BOLD data at 250 Hz using a 1-  
284 dimensional 1st order linear interpolation routine available in Matlab (interp1). This is identical to the  
285 procedure employed by Bettus et al. (2011), who also demonstrated the comparability of  $h^2$  estimates  
286 on highly sampled and normal data.

## 287 288 **2.5 Other metrics: IED count and inter-electrode distance**

289 IEDs counts were calculated automatically with AMADEUS following Bourien et al (2005).  
290 The approach involves detecting abrupt increases (high amplitude, short duration spikes) in the mean  
291 value of the squared modulus of the signal when passed through a wavelet filter bank, enhancing the  
292 fast sharp component of the IED relative to the surrounding background EEG. A single IED count  
293 was associated with each pairwise interaction between electrodes by taking the average of the  
294 individual electrode spike counts. It should be noted that this automated procedure does not  
295 differentiate between paroxysmal activity of different types, and these automatic estimates of IEDs  
296 are distinct from those obtained manually during extended clinical monitoring and used to define  
297 clinical zones.

298 Euclidean distances (mm) were calculated between the centres of each ROI as a proxy for  
299 inter-electrode distances *in situ*.

## 301 2.6 Statistical comparisons

302 The following statistical analyses were performed using JMP version 9 (SAS Institute Inc.,  
303 Cary, NC) on pairwise interactions between electrode/ROIs within the same clinical zone (IZ1, IZ2,  
304 NIZ). Relationships between pairs in different zones were not considered. **Table 2** provides  
305 information regarding the number of pairwise interactions provided within each zone, yielding an  
306 overall sample of n=11543.

307 We were also interested in the extent to which connectivity estimates derived from within  
308 each modality are associated between modalities. We assessed the inter-modal connectivity  
309 correlation (IMCC) via Pearson's r between the sample of pairwise connectivity estimates obtained  
310 from BOLD ROIs ( $h^2_{BOLD}$ ) on the one hand, and the sample of pairwise connectivity estimates derived  
311 from icEEG electrodes ( $h^2_{icEEG}$ ; broadband plus five sub-bands) on the other. The same procedure was  
312 applied between  $vh^2_{BOLD}$  and  $vh^2_{icEEG}$ . Correlation of  $h^2_{BOLD}$  and  $vh^2_{BOLD}$  in relation to IEDs was also  
313 considered. Thus IMCC was investigated for each of the three clinically-defined zones, and  
314 considered significant at a Bonferroni-corrected level of  $0.05/((6+1)*3)=p<0.002$ .

315 Differential impacts of clinically-defined zones on mean  $h^2$  and  $vh^2$  was modelled (ANOVA)  
316 using 'zone' as regressor of interest (3 levels) while controlling for several sources of 'spurious'  
317 variation. Two categorical covariates were included: 'Patient' (9 levels) and 'Electrode Type' (2  
318 levels), the latter reflecting a departure with Bettus et al. (2008; 2011) in which patients were  
319 implanted solely with depth electrodes as in P01, P04 and P09 here, but unlike P06 implanted solely  
320 with grids and all other patients who had a mixture of depth and grid electrodes. Two continuous  
321 covariates, 'IEDs' and 'Euclidean distance' were also included, to account for other possible sources  
322 of variability inherent in the spatial sampling and incidence of paroxysmal activity in epileptic  
323 networks. Tests were compared to two thresholds for significance: an exploratory level of  $p<0.05$ , and  
324 on the assumption of multimodal associations a Bonferroni correction of the number of modalities  
325 (BOLD plus six icEEG bands) threshold of  $0.05/7=p<0.007$ .

### 329 3. RESULTS

#### 330 3.1 Inter-modal connectivity correlations for $h^2$ and $vh^2$

331 **Table 3** lists the observed correlation coefficients and associated p-values. In non-involved  
332 (NIZ) cortices,  $h^2_{\text{BOLD}}$  was significantly positively associated with both  $h^2$  and  $vh^2$  of all frequency  
333 bands measured by our icEEG data. IMCC was strongest in the slower icEEG bands, and weakest at  
334 the highest frequencies studied here.  $h^2_{\text{BOLD}}$  was negatively correlated with  $vh^2_{\text{BOLD}}$ . A negative  
335 association was also exhibited between  $vh^2_{\text{BOLD}}$  and  $vh^2_{\text{icEEG}}$  in the alpha, beta and gamma bands.

336 IMCC as observed in the non-involved region was not found in pathological cortices: no  
337 significant relationships were observed between  $h^2_{\text{BOLD}}$  and  $h^2_{\text{icEEG}}$  outside of the NIZ with the  
338 exception of the delta band in IZ1. Similarly, the only relationship between  $vh^2_{\text{icEEG}}$  and  $vh^2_{\text{BOLD}}$  in  
339 epileptic cortices was a positive correlation observed in the alpha band in IZ2. Finally, while negative  
340 correlations between  $h^2_{\text{BOLD}}$  and  $vh^2_{\text{BOLD}}$  were found in all zones, this negative relationship was  
341 stronger in pathological regions, substantially so for IZ1.

342 Pathological regions also demonstrated relationships not found in unaffected regions. In  
343 particular, significant aberrant negative correlations were found between  $h^2_{\text{icEEG}}$  and  $vh^2_{\text{BOLD}}$  in all  
344 icEEG bands, with the effects being strongest at the highest frequencies.

345 Finally, IEDs were found to be positively correlated with  $vh^2_{\text{BOLD}}$  in IZ2, while correlating  
346 with  $h^2_{\text{BOLD}}$  in IZ1.

#### 347 3.2 Impact of zone on unimodal $h^2$ and $vh^2$

348 While accounting for confounding covariates, significant main effects (Bonferroni-corrected)  
349 of zone were observed on both  $h^2$  and  $vh^2$  for BOLD and across all sub-bands for icEEG-FC (**Table**  
350 **4**). Post-hoc t-tests indicated a differential impact of epileptic processes on FC as well as disjunction  
351 in this impact depending on modality (**Tables 5-6, Figure 2, top**). In particular, IZ1 demonstrated  
352 higher  $h^2_{\text{BOLD}}$ , and IZ2 lower  $h^2_{\text{BOLD}}$  compared to NIZ, while for  $h^2_{\text{icEEG}}$  the inverse pattern was found  
353 across most bands. Across modalities, regions responsible for generating seizures (IZ1) exhibited the  
354 most variance in terms of their respective level of augmentation or disruption relative to the other  
355 zones (**Figure 3, left & right**) and IZ2 exhibited a more consistent relationship with the other zones  
356 (**Figure 3, middle**) of elevated  $h^2_{\text{icEEG}}$  and reduced  $h^2_{\text{BOLD}}$ . This discrepancy between modalities was  
357 also reflected in their variability over the sliding window time series (**Figure 2, bottom**), with  
358 pathological regions exhibiting elevated  $vh^2_{\text{icEEG}}$ , and lower  $vh^2_{\text{BOLD}}$ .

## 361 4. DISCUSSION

362 The current work confirms a previously observed discrepancy between icEEG- and BOLD-  
363 derived FC findings ( $h^2$ ) (Bettus et al. 2008; Bettus et al. 2011) and extends it to FC variability over  
364 time ( $vh^2$ ); in addition, we shed new light on the differential impact of different epileptic processes.  
365 We demonstrate for the first time using simultaneously acquired icEEG-fMRI that epileptic cortices  
366 are distinguished by their internal multimodal resting-state FC as a function of their involvement in  
367 different, clinically-relevant epileptic processes. Furthermore, we provide the first evidence that the  
368 inter-modal connectivity correlation that exists in unaffected regions may be modified in cortices  
369 affected by epileptic pathology, when estimating  $h^2$  and  $vh^2$  in unaffected regions and using invasive  
370 and simultaneous electrophysiological and haemodynamic signals.

### 371 4.1 Inter-modal connectivity correlation in physiological and pathological cortices

372 The non-invasive BOLD signal is an indirect measure of neurological activity, motivating  
373 interest in better understanding its electrophysiological correlates, including in terms of icEEG-  
374 derived connectivity and its relationship to both spontaneous BOLD activity and resting-state  
375 functional connectivity. Correlates from electrophysiological activity (as opposed to connectivity) at  
376 multiple spatial and temporal scales have been proposed (Keilholz 2014; Tagliazucchi and Laufs  
377 2015), with both high-frequency local field potentials (Shmuel and Leopold 2008; Nir et al. 2008;  
378 Schölvinck et al. 2010), and lower frequencies (Lu et al. 2007; He et al. 2008; Pan et al. 2013; Lu et  
379 al. 2016) being advanced as electrophysiological correlates of spontaneous rsfMRI fluctuations.  
380 Others have examined the extent to which connectivity estimates derived from EEG and BOLD are  
381 associated with one another, in terms of the intermodal correlation of the connectivity estimates  
382 derived from each modality. Invasive electrophysiological recordings in rats indicate relationships  
383 between BOLD correlations and EEG band power correlations that are strongest in lower frequency  
384 bands, especially delta, but extending to gamma (Lu et al. 2007; Pan et al. 2011). Modulation by  
385 exogenous stimulation of rsfMRI functional connectivity in rat whisker barrel cortex has been found  
386 to be reflected in the delta range, but not at higher frequencies (Lu et al. 2016). In humans, it has been  
387 shown that BOLD covariance (functional connectivity) matrices can be well explained based on EEG  
388 covariance matrices - similarly so across bands - while the reverse is only true in the lower frequency  
389 bands (Deligianni et al. 2014). Here, in the first study to combine invasive electrophysiological  
390 recording and simultaneous fMRI acquisition, we observe correlations between FC estimated on  
391 haemodynamic and electrophysiological signals across frequency bands in non-involved, ‘healthy’  
392 cortex (**Table 3**). We find the strongest relationships at lower frequencies, possibly reflecting a bias  
393 toward lower bands in maintaining relationships over distant regions due to the relationship between  
394 distance and signal delay (Schölvinck et al. 2013).

396 In contrast, we find almost no evidence of the inter-modality correlation observed in NIZ for  
397  $h^2$  and  $vh^2$  estimates in IZ1 and IZ2. One possibility is that each modality captures a different aspect  
398 of the functional reorganization of networks in the context of epilepsy (Bettus et al. 2010; Bettus et al.  
399 2011; Duncan et al. 2013; Bartolomei et al. 2013b). In this scheme, slow (<0.1Hz) BOLD signal  
400 fluctuations may reflect perturbation of the functional integrity of macro-level intrinsic networks, and  
401 the faster and broader frequency range of EEG to abnormal organisation of epileptic networks poised  
402 to evolve into hypersynchrony at the onset of seizures (Bartolomei et al. 2013a; Bartolomei et al.  
403 2013b) or interictal activity (Centeno and Carmichael 2014). Modification of FC within regions  
404 characterised by involvement in specifically epileptic processes is supported by icEEG (Schevon et al.  
405 2007; Bettus et al. 2008; Bartolomei et al. 2013a; Bartolomei et al. 2013b) and fMRI (Bettus et al.  
406 2011). Additionally, networks thought to reflect intrinsic pattern of connectivity (ICNs), are also  
407 subject to a variety of modifications in epilepsy (Centeno and Carmichael 2014). An apparent  
408 dissociation between interictal electrophysiological and haemodynamic metrics of connectivity in  
409 focal epileptic regions was indicated by Bettus and colleagues (2011) when analysing non-  
410 simultaneous data acquired from the same individuals. They found evidence for a diminution of  
411 functional connectivity within the IZ2 as measured by BOLD, and an augmentation in  $h^2_{icEEG}$  within  
412 IZ1 and IZ2 which was significant in the beta band. Here, using simultaneously-acquired icEEG-  
413 fMRI, we confirm this inter-modality discrepancy in connectivity estimates (**Figure 2, top**), as well as  
414 extending it to the dynamic variability of FC estimates over time (**Figure 2, bottom**). In fMRI  
415 studies investigating connectivity in epilepsy, where ‘involved’ regions are selected on the *a priori*  
416 basis of being likely candidates for involvement in epileptogenesis, a common finding is a reduction  
417 in BOLD-FC (Centeno and Carmichael 2014). To our knowledge, Bettus et al. (2011) is the only  
418 study to have used the specificity of the icEEG gold standard in parallel with BOLD-derived FC  
419 estimates from the same location within the same individuals, and observe a trend to BOLD-FC  
420 reduction in the IZ1 versus NIZ, though it is non-significant. Interestingly, while an inter-modality  
421 discrepancy is also observed in the current results for IZ1, it points in an opposite direction than these  
422 limited antecedents might lead one to expect: an augmentation of BOLD-FC and reduction in icEEG-  
423 FC (**Figure2, top**). While studies that examine BOLD-FC between ICN nodes typically report  
424 decreases in patients, modifications within nodes tell a more complicated story. Not only decreases  
425 but increases in connectivity are evident in the frontal and temporal nodes of multiple ICNs, both for  
426 TLE (He et al. 2008; Liao et al. 2010) and FLE (Braakman et al. 2013; Widjaja et al. 2013). Though  
427 increases have been interpreted as potentially compensatory (Bettus et al. 2009; Bettus et al. 2010;  
428 Ridley et al. 2015), FC increases have also been associated with worse neuropsychological outcomes  
429 (Holmes et al. 2014). In epileptic networks, increases have been seen in the regional homogeneity of  
430 resting BOLD oscillations (Mankinen et al. 2011), and indeed there appears to be a pattern of

connectivity increases reported when it is specifically the vicinity of individually localized epileptogenic regions under consideration. Stuffelbeam et al. (2011) found BOLD-FC increases in local (<5mm) connectivity in proximity to grid electrodes classified as belonging to the seizure onset zone in 5 of 6 patients with focal epilepsy. Similarly, Luo et al. (2014) reported an enhancement of FC in FLE patients in the immediate neighbourhood of cortical epileptogenic zones defined by EEG-fMRI data fusion.

We note that the variability in findings observed across the literature in ‘epileptogenic’ regions is reflected in the inter-individual variability of FC estimates (**Figure 3, left**) and differences between IZ1 and non-involved zones in our sample (**Figure 3, right**). Insofar as modifications to connectivity in epileptic networks which are salient to different modalities might reflect different disease process, as suggested above, the extent to which these might interact with different aetiologies is unknown, and is an area that should receive further attention. Indeed, a recent analysis of magnetoencephalography data in both mesial TLE and focal neocortical patients indicates a mixture of focal increases and decreases in pre-surgery FC in epileptogenic regions that would later undergo resection (putative IZ1) versus non-involved homologous regions in the contralateral hemisphere (Englot et al. 2015). In contrast, the IZ2 may represent a more similar situation across individuals than IZ1 (**Figure 3, IZ2-NIZ contrast**), as relatively ‘healthy’ cortex extending beyond focal lesions that is not so degenerate as to self-generate seizures, and where IEDs are the main form of pathological activity impinging on brain networks. For example, while metabolic abnormalities suggestive of defective neurovascular coupling are observed in IZ2 (Guye et al. 2002; Guye et al. 2005), they are reversible as seen in post-operative patients who have become seizure free after successful resection surgery (Serles et al. 2001). This difference in the relationship to ongoing disease processes may be reflected in the fact that IEDs appear to be disruptive to  $h^2_{\text{BOLD}}$  connectivity leading to its reduction in IZ2 (**Figure 2, top**) and greater variability as measured by  $vh^2_{\text{icEEG}}$  (**Figure 2, bottom and Table 2**), versus the positive correlation observed between IEDs and  $vh^2_{\text{BOLD}}$  and the anti-correlation of  $vh^2_{\text{BOLD}}$  and  $h^2_{\text{icEEG}}$  (**Table 3**).

#### 4.2 Altered neurovascular coupling in pathological cortices

Altered neurovascular coupling has been proposed as an explanation of apparent discrepancies between icEEG- and BOLD-derived indices of FC (Bettus et al. 2011), and might also play a role in the absence of correlation seen here. Metabolic anomalies in electrophysiologically abnormal regions have been demonstrated in both TLE (Guye et al. 2002) and FLE (Guye et al. 2005), with the addition of both vascularisation defects (Duncan 2010) and blood-brain barrier dysfunctions in TLE (Oby and Janigro 2006). Furthermore, evidence from rat models suggests that neurovascular coupling is comparable between evoked and spontaneous BOLD oscillations (Bruyns-

466 Haylett et al. 2013), but that evoked neurovascular coupling is modified during ictal epileptic activity  
467 (Harris et al. 2013). This is suggestive of a broad comparability between spontaneous and evoked  
468 neurovascular coupling which may be subject to modification in the context of epilepsy.

469 Our results suggest that multimodal differences persist despite an equivalent *incidence* of  
470 inter-modal between-session factors (as ensured by simultaneous acquisition), though this in itself  
471 does not exclude a difference in *impact* between modalities. Modelling may be one means of  
472 understanding how such differences contribute to the discrepancies seen here, but it should be noted  
473 that the choice of parameters derived from one signal for the understating of another is highly non-  
474 trivial. For example, an argument for a disruptive effect of interictal epileptic transients such as IEDs  
475 on connectivity has a *prima facie* plausibility. However, empirical results have been more equivocal  
476 with negative (Nissen et al. 2016), positive (Bartolomei et al. 2013a) and null (Bettus et al. 2008)  
477 associations of IEDs with FC in epileptics networks observed in scalp and invasive electrophysiology,  
478 but also overall limited-to-no-effect of removing IED-containing epochs by censoring data (Bettus et  
479 al. 2008; Warren et al. 2010b; Bartolomei et al. 2013a). On the other hand, general linear modelling of  
480 IEDs and other epileptic transient provided some of the earliest evidence of an interaction of epilepsy  
481 with resting-state phenomena in the form of IED- and seizure-associated BOLD changes in regions  
482 associated with intrinsic connectivity networks, most especially the default mode network (Gotman  
483 and Pittau 2011; van Graan et al. 2015). Interictal phenomena may be associated with increases,  
484 decreases or unchanged BOLD signal (Béнар et al., 2006; Salek-Haddadi et al., 2006; Stefan and  
485 Lopes da Silva, 2013; Thornton et al., 2011), and BOLD changes may be found in regions with no  
486 apparent involvement on EEG (Kobayashi et al. 2006). Interpreting the variability of these results is  
487 further complicated by recent evidence that coupling is state- and time-dependant in addition to being  
488 spatially organized in the resting-state (Feige et al. 2016). While suggestive of a framework for  
489 understanding the differential impact between modalities, how altered coupling might pertain to the  
490 findings in the current study - the focus of which is FC in epileptic networks rather than resting  
491 activity in ICNs per se - is unclear. Indeed, there is evidence of dissociation between different means  
492 of characterizing resting state activity in epilepsy, with discordant finding in terms of the amplitude  
493 and connectivity of resting state activity in the same patients (Zhang et al. 2015). As noted above,  
494 multiple processes that contribute to neurovascular coupling and hence the BOLD-signal generation  
495 cascade are effected in epilepsy, and as such represent sources of unmodeled noise standing between  
496 underlying processes and the signals as estimated via such metrics as (de-)activation or connectivity.  
497 The separate contributions of perfusion deficits (Duncan 2009) and altered metabolic demands in the  
498 chronic epileptic state and under the specific influence of epileptic transients will likely need to be  
499 characterized. Multimodal exploration as traditionally performed and in new combinations is one tool

500 to mutually constrain different sources of non-neuronal noise and mutually support conclusions by  
501 filling in missing information (Uludağ and Roebroeck 2014).

### 503 **4.3 Multimodal relationships of time varying FC**

504 In addition to establishing a relationship between indices of connectivity in simultaneous  
505 icEEG and fMRI data, sliding window analyses allowed us to resolve the variability of connectivity  
506 over time. Comparable analyses have been applied previously to fMRI data in temporal lobe epilepsy  
507 patients, showing modifications in time-resolved connectivity associated with disease burden of  
508 memory scores (Douw et al. 2015), and both increases (Laufs et al. 2014) and decreases (Nedic et al.  
509 2015) in the variability of FC in regions that might plausibly be considered part of epileptic networks  
510 on an *a priori* basis. Current results, in regions assigned to IZ1 and IZ2 by the electrophysiological  
511 gold standard, tend to agree with the latter:  $vh^2_{\text{BOLD}}$  is significantly reduced in IZ1 (**Figure 2**).  
512 Furthermore, we provide the first simultaneous icEEG-fMRI evidence in humans of an inter-modality  
513 discrepancy in the variability of FC over time in epileptic regions: in opposition to BOLD,  $vh^2$   
514 estimates derived from icEEG indicate an augmentation across bands in irritative regions, and  
515 specifically in IZ1 in alpha, beta and gamma bands.

516 Our findings indicate that in healthy cortex BOLD  $h^2$  is related to  $vh^2_{\text{icEEG}}$  across sub-bands,  
517 but that BOLD  $vh^2$  shows a relationship to icEEG  $vh^2$  only in alpha, beta and gamma bands (**Table 3**).  
518 Both findings may reflect the imbalance when trying to predict FC in one modality from the other  
519 (Deligianni et al. 2014), with variability in all icEEG bands imparting information about BOLD  
520 connectivity oscillations, but the inverse not being the case. This is in good agreement with previous  
521 work indicating covariation in correlation between modalities in comparable bands in rat and macaque  
522 studies (Magri et al. 2012; Thompson et al. 2013), and possibly reflects the widely hypothesized role  
523 of alpha and gamma bands in particular in communication between neural assemblies at distal and  
524 local scales, respectively (Keilholz 2014). As with multimodal relationships between estimates of  
525 connectivity, multimodal relationships in the variability in FC across sliding window timeseries  
526 appear to be disrupted in pathological cortices in epilepsy.

527 Whole brain computational simulation approaches comparing empirical data to simulated  
528 functional data derived from structural models suggest that the agreement between simulated and  
529 empirical data are best when both a low energy spontaneous state and several states of localized high  
530 activity are stable states of the system (Cabral et al. 2014). In this context, slow resting-state  
531 oscillations represent the dynamic exploration of the different states of the brain's intrinsic functional  
532 repertoire instigated by underlying anatomic connectivity and intrinsic noise (Deco and Jirsa 2012).  
533 This could maintain the brain in a state of heightened competition ready to evolve momentarily into a  
534 specific state under the influence of internal or external sensory modulation (Deco and Corbetta



2011). Our results show that IZ1 is associated with both an augmentation of  $h^2_{\text{BOLD}}$  and a reduction in  $vh^2_{\text{BOLD}}$ . This could reflect a dynamic repertoire that is reduced in diseased cortices under the influence of both epileptogenic processes and paroxysmal interictal activity, with a propensity toward seizures being one of the states that such influences promote. If a reduced repertoire reflects homogeneity in self-sustaining pathological oscillatory states, this could be reflected in both abnormally high FC and less rich dynamics, consistent with the negative relationship between  $h^2$  and  $vh^2$  of BOLD which we find to be augmented in irritative cortices and at its highest in IZ1. In contrast, IZ2 may represent cortex that is less degenerate in this sense – showing no reduction in  $vh^2_{\text{BOLD}}$  compared to NIZ – but is chronically subject to disruption by interictal transients which could be reflected in the correlation of IEDs and  $vh^2_{\text{BOLD}}$  (**Table 3**).

#### 4.4. Limitations and Future Directions

The implantation, placement and coverage of intracranial electrodes are motivated first and foremost by clinical necessity, leading to a degree of heterogeneity in our sample. We have attempted to identify and account for several forms of heterogeneity via quantitative proxies including Euclidean distance and automatically-generated IED counts. For example, since the automatic extraction of IEDs is based on locating abrupt and transient signal modulations there is a possibility of misidentifying non-pathological transients as IEDs, as is also the case for manually defined IEDs (Noachtar and Rémi 2009). **Supplementary Figure 1** shows the number of ‘IEDs’ identified by zone at group and individual levels, and though the relative amounts of ‘IEDs’ detected by the algorithm meet clinical expectations (Bartolomei et al. 2016), a small amount were located in regions classified as NIZ based on experienced clinical analysis. It is likely that these proxies account for only some of the variance involved in estimating connectivity in epilepsy, and more exact measures of propagation distance and a more discerning treatment of different types of interictal electrophysiological phenomena may provide further insights. Additionally, a development of the current work could involve the normalization of BOLD-FC against estimates derived from controls using the ROIs extracted from the electrodes in each patient, to allow the demarcation of differences deriving from spatial sampling and pathology. Other potential influences on FC could be considered as well, including anti-epileptic medications as patients were continued on their normal regimen and were not reduced at the time of scan

While simultaneously acquired icEEG-fMRI has the benefit of avoiding the confound of separate acquisitions, it is not without its own technical challenges (Carmichael et al. 2010; Carmichael et al. 2012). In particular, reduction in BOLD signal can occur around electrodes due to the difference in magnetic susceptibility between electrode and tissue in the presence of the scanner’s strong magnetic field. A validation study by Carmichael and colleagues (Carmichael et al. 2012)

570 found that signal reduction was similar for depth and grid electrodes, and was on average less than  
1 571 50% at 5mm from the electrode, the radius of the ROIs used here. Similarly, data from simultaneous  
2  
3 572 EEG-fMRI studies suggests minimal disturbances of temporal signal to noise ratios, with comparable  
4  
5 573 detectability of activation fMRI time-courses in the presence and absence of EEG recording  
6  
7 574 acquisition during fMRI (Luo and Glover 2012). Given the points of consistency our BOLD results  
8  
9 575 share with previous non-simultaneous icEEG-fMRI and unimodal fMRI data (Bettus et al. 2009;  
10 576 Bettus et al. 2011; Mankinen et al. 2011; Stufflebeam et al. 2011; Luo et al. 2014), signal drop-out  
11  
12 577 due to electrodes seems unlikely to be a crucial factor in this work. Our results tend to suggest that  
13  
14 578 despite the loss of MRI signal in the immediate vicinity of the electrodes, the observed effects extend  
15  
16 579 to a large enough brain area beyond the region of drop out around each electrode.

17 580 Finally, while we have examined the variability of FC over time for a sliding window  
18 581 analysis, it should be acknowledged that establishing true dynamics requires a demonstration of a  
19  
20 582 distinction with random fluctuations, and that this is particularly controversial in the context of  
21  
22 583 fluctuations in BOLD-derived FC (Keilholz 2014). That said, we demonstrate relationships between  
23  
24 584 haemodynamic and electrophysiological indices of variation and connectivity suggesting that at least  
25  
26 585 some part of the fluctuation in BOLD connectivity reflects a neural origin.

27 586

587 **5. Conclusion**

1 588 We provide the first evidence derived from intracranial EEG and simultaneous BOLD signals  
2  
3 589 of inter-modality correlation in healthy human cortex in terms of both static functional connectivity  
4  
5 590 and its time-resolved variability. Furthermore, while ruling out differences in the intra-individual  
6  
7 591 incidence of non-stationarities, we observe a lack of inter-modality connectivity correlation in regions  
8  
9 592 subject to epileptic processes, with a confirmation of inter-modality discrepancies in functional  
10  
11 593 connectivity associated with epileptic cortices while establishing for the first time that this  
12  
13 594 discrepancy extends to the dynamical variability of connectivity over time.

14 595

596 **References**

- 1  
2 597 Allen PJ, Josephs O, Turner R (2000) A method for removing imaging artifact from continuous EEG  
3 598 recorded during functional MRI. *NeuroImage* 12:230–239. doi: 10.1006/nimg.2000.0599  
4  
5 599 Bartolomei F, Bettus G, Stam CJ, Guye M (2013a) Interictal network properties in mesial temporal  
6 600 lobe epilepsy: A graph theoretical study from intracerebral recordings. *Clin Neurophysiol Off*  
7 601 *J Int Fed Clin Neurophysiol*. doi: 10.1016/j.clinph.2013.06.003  
8  
9  
10 602 Bartolomei F, Guye M, Wendling F (2013b) Abnormal binding and disruption in large scale networks  
11 603 involved in human partial seizures. *EPJ Nonlinear Biomed Phys* 1:1–16. doi:  
12 604 10.1140/epjnbp11  
13  
14 605 Bartolomei F, Trébuchon A, Bonini F, et al (2016) What is the concordance between the seizure onset  
15 606 zone and the irritative zone? A SEEG quantified study. *Clin Neurophysiol Off J Int Fed Clin*  
16 607 *Neurophysiol* 127:1157–1162. doi: 10.1016/j.clinph.2015.10.029  
17  
18  
19 608 Bettus G, Bartolomei F, Confort-Gouny S, et al (2010) Role of resting state functional connectivity  
20 609 MRI in presurgical investigation of mesial temporal lobe epilepsy. *J Neurol Neurosurg*  
21 610 *Psychiatry* 81:1147–1154. doi: 10.1136/jnnp.2009.191460  
22  
23 611 Bettus G, Guedj E, Joyeux F, et al (2009) Decreased basal fMRI functional connectivity in  
24 612 epileptogenic networks and contralateral compensatory mechanisms. *Hum Brain Mapp*  
25 613 30:1580–1591. doi: 10.1002/hbm.20625  
26  
27 614 Bettus G, Ranjeva J-P, Wendling F, et al (2011) Interictal functional connectivity of human epileptic  
28 615 networks assessed by intracerebral EEG and BOLD signal fluctuations. *PLoS One* 6:e20071.  
29 616 doi: 10.1371/journal.pone.0020071  
30  
31  
32 617 Bettus G, Wendling F, Guye M, et al (2008) Enhanced EEG functional connectivity in mesial  
33 618 temporal lobe epilepsy. *Epilepsy Res* 81:58–68. doi: 10.1016/j.eplepsyres.2008.04.020  
34  
35 619 Bourien J, Bartolomei F, Bellanger JJ, et al (2005) A method to identify reproducible subsets of co-  
36 620 activated structures during interictal spikes. Application to intracerebral EEG in temporal lobe  
37 621 epilepsy. *Clin Neurophysiol Off J Int Fed Clin Neurophysiol* 116:443–455. doi:  
38 622 10.1016/j.clinph.2004.08.010  
39  
40  
41 623 Braakman HMH, Vaessen MJ, Jansen JFA, et al (2013) Frontal lobe connectivity and cognitive  
42 624 impairment in pediatric frontal lobe epilepsy. *Epilepsia* 54:446–454. doi: 10.1111/epi.12044  
43  
44 625 Bruyins-Haylett M, Harris S, Boorman L, et al (2013) The resting-state neurovascular coupling  
45 626 relationship: rapid changes in spontaneous neural activity in the somatosensory cortex are  
46 627 associated with haemodynamic fluctuations that resemble stimulus-evoked haemodynamics.  
47 628 *Eur J Neurosci* 38:2902–2916. doi: 10.1111/ejn.12295  
48  
49  
50 629 Cabral J, Kringelbach ML, Deco G (2014) Exploring the network dynamics underlying brain activity  
51 630 during rest. *Prog Neurobiol* 114:102–131. doi: 10.1016/j.pneurobio.2013.12.005  
52  
53 631 Carmichael DW, Thornton JS, Rodionov R, et al (2010) Feasibility of simultaneous intracranial EEG-  
54 632 fMRI in humans: a safety study. *NeuroImage* 49:379–390. doi:  
55 633 10.1016/j.neuroimage.2009.07.062  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

- 634 Carmichael DW, Vulliemoz S, Rodionov R, et al (2012) Simultaneous intracranial EEG-fMRI in  
1 635 humans: protocol considerations and data quality. *NeuroImage* 63:301–309. doi:  
2 636 10.1016/j.neuroimage.2012.05.056  
3
- 4 637 Casdagli MC, Iasemidis LD, Savit RS, et al (1997) Non-linearity in invasive EEG recordings from  
5 638 patients with temporal lobe epilepsy. *Electroencephalogr Clin Neurophysiol* 102:98–105.  
6
- 7 639 Centeno M, Carmichael DW (2014) Network connectivity in epilepsy: resting state fMRI and EEG–  
8 640 fMRI contributions. *Epilepsy* 5:93. doi: 10.3389/fneur.2014.00093  
9
- 10  
11 641 Chauvel P (2001) Contributions of Jean Talairach and Jean Bancaud to epilepsy surgery. In: Luders  
12 642 H, Comair YG (eds) *Epilepsy Surgery*. Lippincott Williams & Wilkins, Philadelphia, pp 35–  
13 643 41  
14
- 15 644 Deco G, Corbetta M (2011) The dynamical balance of the brain at rest. *Neurosci Rev J Bringing*  
16 645 *Neurobiol Neurol Psychiatry* 17:107–123. doi: 10.1177/1073858409354384  
17
- 18 646 Deco G, Jirsa VK (2012) Ongoing cortical activity at rest: criticality, multistability, and ghost  
19 647 attractors. *J Neurosci Off J Soc Neurosci* 32:3366–3375. doi: 10.1523/JNEUROSCI.2523-  
20 648 11.2012  
21  
22
- 23 649 Deligianni F, Centeno M, Carmichael DW, Clayden JD (2014) Relating resting-state fMRI and EEG  
24 650 whole-brain connectomes across frequency bands. *Front Neurosci* 8:258. doi:  
25 651 10.3389/fnins.2014.00258  
26
- 27 652 Douw L, Leveroni CL, Tanaka N, et al (2015) Loss of resting-state posterior cingulate flexibility is  
28 653 associated with memory disturbance in left temporal lobe epilepsy. *PLoS One* 10:e0131209.  
29 654 doi: 10.1371/journal.pone.0131209  
30
- 31  
32 655 Duncan D, Duckrow RB, Pincus SM, et al (2013) Intracranial EEG evaluation of relationship within a  
33 656 resting state network. *Clin Neurophysiol Off J Int Fed Clin Neurophysiol* 124:1943–1951.  
34 657 doi: 10.1016/j.clinph.2013.03.028  
35
- 36 658 Duncan J (2009) The current status of neuroimaging for epilepsy. *Curr Opin Neurol* 22:179–184. doi:  
37 659 10.1097/WCO.0b013e328328f260  
38
- 39 660 Duncan JS (2010) Imaging in the surgical treatment of epilepsy. *Nat Rev Neurol* 6:537–550. doi:  
40 661 10.1038/nrneurol.2010.131  
41
- 42  
43 662 Duncan NW, Northoff G (2013) Overview of potential procedural and participant-related confounds  
44 663 for neuroimaging of the resting state. *J Psychiatry Neurosci JPN* 38:84–96. doi:  
45 664 10.1503/jpn.120059  
46
- 47 665 Englot DJ, Hinkley LB, Kort NS, et al (2015) Global and regional functional connectivity maps of  
48 666 neural oscillations in focal epilepsy. *Brain J Neurol* 138:2249–2262. doi:  
49 667 10.1093/brain/awv130  
50
- 51  
52 668 Feige B, Spiegelhalter K, Kiemen A, et al (2016) Distinctive time-lagged resting-state networks  
53 669 revealed by simultaneous EEG-fMRI. *NeuroImage*. doi: 10.1016/j.neuroimage.2016.09.027  
54
- 55 670 Garrett DD, Kovacevic N, McIntosh AR, Grady CL (2013) The modulation of BOLD variability  
56 671 between cognitive states varies by age and processing speed. *Cereb Cortex N Y N* 1991  
57 672 23:684–693. doi: 10.1093/cercor/bhs055  
58  
59  
60  
61  
62  
63  
64  
65

- 673 Garrett DD, Kovacevic N, McIntosh AR, Grady CL (2010) Blood oxygen level-dependent signal  
1 674 variability is more than just noise. *J Neurosci Off J Soc Neurosci* 30:4914–4921. doi:  
2 675 10.1523/JNEUROSCI.5166-09.2010  
3
- 4 676 Gotman J, Pittau F (2011) Combining EEG and fMRI in the study of epileptic discharges. *Epilepsia*  
5 677 52 Suppl 4:38–42. doi: 10.1111/j.1528-1167.2011.03151.x  
6
- 7 678 Guye M, Bartolomei F, Ranjeva J-P (2008) Imaging structural and functional connectivity: towards a  
8 679 unified definition of human brain organization? *Curr Opin Neurol* 21:393–403. doi:  
9 680 10.1097/WCO.0b013e3283065cfb  
10
- 11 681 Guye M, Bettus G, Bartolomei F, Cozzone PJ (2010) Graph theoretical analysis of structural and  
12 682 functional connectivity MRI in normal and pathological brain networks. *Magma N Y N*  
13 683 23:409–421. doi: 10.1007/s10334-010-0205-z  
14  
15
- 16 684 Guye M, Le Fur Y, Confort-Gouny S, et al (2002) Metabolic and electrophysiological alterations in  
17 685 subtypes of temporal lobe epilepsy: a combined proton magnetic resonance spectroscopic  
18 686 imaging and depth electrodes study. *Epilepsia* 43:1197–1209.  
19
- 20 687 Guye M, Ranjeva JP, Le Fur Y, et al (2005) <sup>1</sup>H-MRS imaging in intractable frontal lobe epilepsies  
21 688 characterized by depth electrode recording. *NeuroImage* 26:1174–1183. doi:  
22 689 10.1016/j.neuroimage.2005.03.023  
23  
24
- 25 690 Harris S, Bruyns-Haylett M, Kennerley A, et al (2013) The effects of focal epileptic activity on  
26 691 regional sensory-evoked neurovascular coupling and postictal modulation of bilateral sensory  
27 692 processing. *J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab* 33:1595–1604.  
28 693 doi: 10.1038/jcbfm.2013.115  
29
- 30 694 He BJ, Snyder AZ, Zempel JM, et al (2008) Electrophysiological correlates of the brain's intrinsic  
31 695 large-scale functional architecture. *Proc Natl Acad Sci U S A* 105:16039–16044. doi:  
32 696 10.1073/pnas.0807010105  
33  
34
- 35 697 Holmes M, Folley BS, Sonmezturk HH, et al (2014) Resting state functional connectivity of the  
36 698 hippocampus associated with neurocognitive function in left temporal lobe epilepsy. *Hum*  
37 699 *Brain Mapp* 35:735–744. doi: 10.1002/hbm.22210  
38
- 39 700 Kaneoke Y, Donishi T, Iwatani J, et al (2012) Variance and autocorrelation of the spontaneous slow  
40 701 brain activity. *PLoS One* 7:e38131. doi: 10.1371/journal.pone.0038131  
41  
42
- 43 702 Keilholz SD (2014) The neural basis of time-varying resting-state functional connectivity. *Brain*  
44 703 *Connect* 4:769–779. doi: 10.1089/brain.2014.0250  
45
- 46 704 Kobayashi E, Bagshaw AP, Grova C, et al (2006) Negative BOLD responses to epileptic spikes. *Hum*  
47 705 *Brain Mapp* 27:488–497. doi: 10.1002/hbm.20193  
48
- 49 706 Laufs H (2012) Functional imaging of seizures and epilepsy: evolution from zones to networks. *Curr*  
50 707 *Opin Neurol* 25:194–200. doi: 10.1097/WCO.0b013e3283515db9  
51
- 52 708 Laufs H, Rodionov R, Thornton R, et al (2014) Altered FMRI connectivity dynamics in temporal lobe  
53 709 epilepsy might explain seizure semiology. *Front Neurol* 5:175. doi:  
54 710 10.3389/fneur.2014.00175  
55  
56
- 57 711 Liao W, Zhang Z, Pan Z, et al (2010) Altered functional connectivity and small-world in mesial  
58 712 temporal lobe epilepsy. *PLoS One* 5:e8525. doi: 10.1371/journal.pone.0008525  
59  
60  
61  
62  
63  
64  
65

713 Lopes R, Moeller F, Besson P, et al (2014) Study on the Relationships between Intrinsic Functional  
1 714 Connectivity of the Default Mode Network and Transient Epileptic Activity. *Front Neurol*  
2 715 5:201. doi: 10.3389/fneur.2014.00201  
3

4 716 Lu H, Wang L, Rea WW, et al (2016) Low- but Not High-Frequency LFP Correlates with  
5 717 Spontaneous BOLD Fluctuations in Rat Whisker Barrel Cortex. *Cereb Cortex N Y N 1991*  
6 718 26:683–694. doi: 10.1093/cercor/bhu248  
7

8 719 Lu H, Zuo Y, Gu H, et al (2007) Synchronized delta oscillations correlate with the resting-state  
9 720 functional MRI signal. *Proc Natl Acad Sci U S A* 104:18265–18269. doi:  
10 721 10.1073/pnas.0705791104  
11

12 722 Luo C, An D, Yao D, Gotman J (2014) Patient-specific connectivity pattern of epileptic network in  
13 723 frontal lobe epilepsy. *NeuroImage Clin* 4:668–675. doi: 10.1016/j.nicl.2014.04.006  
14  
15

16 724 Luo Q, Glover GH (2012) Influence of dense-array EEG cap on fMRI signal. *Magn Reson Med*  
17 725 68:807–815. doi: 10.1002/mrm.23299  
18

19 726 Magri C, Schridde U, Murayama Y, et al (2012) The amplitude and timing of the BOLD signal  
20 727 reflects the relationship between local field potential power at different frequencies. *J*  
21 728 *Neurosci Off J Soc Neurosci* 32:1395–1407. doi: 10.1523/JNEUROSCI.3985-11.2012  
22  
23

24 729 Mankinen K, Long X-Y, Paakki J-J, et al (2011) Alterations in regional homogeneity of baseline brain  
25 730 activity in pediatric temporal lobe epilepsy. *Brain Res* 1373:221–229. doi:  
26 731 10.1016/j.brainres.2010.12.004  
27

28 732 Nedic S, Stufflebeam SM, Rondinoni C, et al (2015) Using network dynamic fMRI for detection of  
29 733 epileptogenic foci. *BMC Neurol* 15:262. doi: 10.1186/s12883-015-0514-y  
30

31 734 Netoff TI, Pecora LM, Schiff SJ (2004) Analytical coupling detection in the presence of noise and  
32 735 nonlinearity. *Phys Rev E Stat Nonlin Soft Matter Phys* 69:017201. doi:  
33 736 10.1103/PhysRevE.69.017201  
34  
35

36 737 Nir Y, Mukamel R, Dinstein I, et al (2008) Interhemispheric correlations of slow spontaneous  
37 738 neuronal fluctuations revealed in human sensory cortex. *Nat Neurosci* 11:1100–1108.  
38

39 739 Nissen IA, van Klink NEC, Zijlmans M, et al (2016) Brain areas with epileptic high frequency  
40 740 oscillations are functionally isolated in MEG virtual electrode networks. *Clin Neurophysiol*  
41 741 *Off J Int Fed Clin Neurophysiol* 127:2581–2591. doi: 10.1016/j.clinph.2016.04.013  
42

43 742 Noachtar S, Rémi J (2009) The role of EEG in epilepsy: a critical review. *Epilepsy Behav* EB 15:22–  
44 743 33. doi: 10.1016/j.yebeh.2009.02.035  
45  
46

47 744 Oby E, Janigro D (2006) The blood-brain barrier and epilepsy. *Epilepsia* 47:1761–1774. doi:  
48 745 10.1111/j.1528-1167.2006.00817.x  
49

50 746 Palmi A (2006) The concept of the epileptogenic zone: a modern look at Penfield and Jasper’s  
51 747 views on the role of interictal spikes. *Epileptic Disord Int Epilepsy J Videotape* 8 Suppl  
52 748 2:S10-15.  
53

54 749 Pan W-J, Thompson G, Magnuson M, et al (2011) Broadband local field potentials correlate with  
55 750 spontaneous fluctuations in functional magnetic resonance imaging signals in the rat  
56 751 somatosensory cortex under isoflurane anesthesia. *Brain Connect* 1:119–131. doi:  
57 752 10.1089/brain.2011.0014  
58  
59

- 1 753 Pan W-J, Thompson GJ, Magnuson ME, et al (2013) Infralow LFP correlates to resting-state fMRI  
2 754 BOLD signals. *NeuroImage* 74:288–297. doi: 10.1016/j.neuroimage.2013.02.035
- 3 755 Power JD, Barnes KA, Snyder AZ, et al (2012) Spurious but systematic correlations in functional  
4 756 connectivity MRI networks arise from subject motion. *NeuroImage* 59:2142–2154. doi:  
5 757 10.1016/j.neuroimage.2011.10.018
- 6  
7 758 Raichle ME (2015) The restless brain: how intrinsic activity organizes brain function. *Philos Trans R*  
8 759 *Soc Lond B Biol Sci*. doi: 10.1098/rstb.2014.0172
- 9  
10  
11 760 Ridley BGY, Rousseau C, Wirsich J, et al (2015) Nodal approach reveals differential impact of  
12 761 lateralized focal epilepsies on hub reorganization. *NeuroImage* 118:39–48. doi:  
13 762 10.1016/j.neuroimage.2015.05.096
- 14  
15 763 Rosenow F, Lüders H (2001) Presurgical evaluation of epilepsy. *Brain J Neurol* 124:1683–1700.
- 16  
17 764 Schevon CA, Cappell J, Emerson R, et al (2007) Cortical abnormalities in epilepsy revealed by local  
18 765 EEG synchrony. *NeuroImage* 35:140–148. doi: 10.1016/j.neuroimage.2006.11.009
- 19  
20  
21 766 Schölvinck ML, Leopold DA, Brookes MJ, Khader PH (2013) The contribution of electrophysiology  
22 767 to functional connectivity mapping. *NeuroImage* 80:297–306. doi:  
23 768 10.1016/j.neuroimage.2013.04.010
- 24  
25 769 Schölvinck ML, Maier A, Ye FQ, et al (2010) Neural basis of global resting-state fMRI activity. *Proc*  
26 770 *Natl Acad Sci U S A* 107:10238–10243. doi: 10.1073/pnas.0913110107
- 27  
28 771 Serles W, Li LM, Antel SB, et al (2001) Time course of postoperative recovery of N-acetyl-aspartate  
29 772 in temporal lobe epilepsy. *Epilepsia* 42:190–197.
- 30  
31  
32 773 Shmuel A, Leopold DA (2008) Neuronal correlates of spontaneous fluctuations in fMRI signals in  
33 774 monkey visual cortex: Implications for functional connectivity at rest. *Hum Brain Mapp*  
34 775 29:751–761. doi: 10.1002/hbm.20580
- 35  
36 776 Smith SM, Fox PT, Miller KL, et al (2009) Correspondence of the brain’s functional architecture  
37 777 during activation and rest. *Proc Natl Acad Sci U S A* 106:13040–13045. doi:  
38 778 10.1073/pnas.0905267106
- 39  
40  
41 779 Spencer SS (2002) Neural networks in human epilepsy: evidence of and implications for treatment.  
42 780 *Epilepsia* 43:219–227.
- 43  
44 781 Sporns O (2014) Contributions and challenges for network models in cognitive neuroscience. *Nat*  
45 782 *Neurosci* 17:652–660. doi: 10.1038/nn.3690
- 46  
47 783 Stufflebeam SM, Liu H, Sepulcre J, et al (2011) Localization of focal epileptic discharges using  
48 784 functional connectivity magnetic resonance imaging. *J Neurosurg* 114:1693–1697. doi:  
49 785 10.3171/2011.1.JNS10482
- 50  
51  
52 786 Tagliazucchi E, Laufs H (2015) Multimodal imaging of dynamic functional connectivity. *Front*  
53 787 *Neurol* 6:10. doi: 10.3389/fneur.2015.00010
- 54  
55 788 Thompson GJ, Merritt MD, Pan W-J, et al (2013) Neural correlates of time-varying functional  
56 789 connectivity in the rat. *NeuroImage* 83:826–836. doi: 10.1016/j.neuroimage.2013.07.036



790 Uludağ K, Roebroek A (2014) General overview on the merits of multimodal neuroimaging data  
1 791 fusion. *NeuroImage* 102 Pt 1:3–10. doi: 10.1016/j.neuroimage.2014.05.018  
2

3 792 van Diessen E, Numan T, van Dellen E, et al (2015) Opportunities and methodological challenges in  
4 793 EEG and MEG resting state functional brain network research. *Clin Neurophysiol Off J Int*  
5 794 *Fed Clin Neurophysiol* 126:1468–1481. doi: 10.1016/j.clinph.2014.11.018  
6

7 795 van Graan LA, Lemieux L, Chaudhary UJ (2015) Methods and utility of EEG-fMRI in epilepsy.  
8 796 *Quant Imaging Med Surg* 5:300–312. doi: 10.3978/j.issn.2223-4292.2015.02.04  
9

10  
11 797 Vulliemoz S, Carmichael DW, Rosenkranz K, et al (2011) Simultaneous intracranial EEG and fMRI  
12 798 of interictal epileptic discharges in humans. *NeuroImage* 54:182–190. doi:  
13 799 10.1016/j.neuroimage.2010.08.004  
14

15 800 Warren CP, Hu S, Stead M, et al (2010a) Synchrony in normal and focal epileptic brain: the seizure  
16 801 onset zone is functionally disconnected. *J Neurophysiol* 104:3530–3539. doi:  
17 802 10.1152/jn.00368.2010  
18

19 803 Warren CP, Hu S, Stead M, et al (2010b) Synchrony in normal and focal epileptic brain: the seizure  
20 804 onset zone is functionally disconnected. *J Neurophysiol* 104:3530–3539. doi:  
21 805 10.1152/jn.00368.2010  
22  
23

24 806 Wendling F (2015) Software Amadeus-Visualisation. Inserm-Université de Rennes 1.  
25 807 FR.001.420017.000.S.P.2015.000.31230  
26

27 808 Wendling F, Bartolomei F, Bellanger JJ, Chauvel P (2001) [Identification of epileptogenic networks  
28 809 from modeling and nonlinear analysis of SEEG signals]. *Neurophysiol Clin Clin*  
29 810 *Neurophysiol* 31:139–151.  
30

31  
32 811 Wendling F, Chauvel P, Biraben A, Bartolomei F (2010) From intracerebral EEG signals to brain  
33 812 connectivity: identification of epileptogenic networks in partial epilepsy. *Front Syst Neurosci*  
34 813 4:154. doi: 10.3389/fnsys.2010.00154  
35

36 814 Widjaja E, Zamyadi M, Raybaud C, et al (2013) Abnormal functional network connectivity among  
37 815 resting-state networks in children with frontal lobe epilepsy. *AJNR Am J Neuroradiol*  
38 816 34:2386–2392. doi: 10.3174/ajnr.A3608  
39

40 817 Xia M, Wang J, He Y (2013) BrainNet Viewer: A Network Visualization Tool for Human Brain  
41 818 Connectomics. *PLoS ONE*. doi: 10.1371/journal.pone.0068910  
42

43  
44 819 Zhang Z, Lu G, Zhong Y, et al (2010) fMRI study of mesial temporal lobe epilepsy using amplitude  
45 820 of low-frequency fluctuation analysis. *Hum Brain Mapp* 31:1851–1861. doi:  
46 821 10.1002/hbm.20982  
47

48 822 Zhang Z, Xu Q, Liao W, et al (2015) Pathological uncoupling between amplitude and connectivity of  
49 823 brain fluctuations in epilepsy. *Hum Brain Mapp* 36:2756–2766. doi: 10.1002/hbm.22805  
50

51 824  
52  
53 825  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

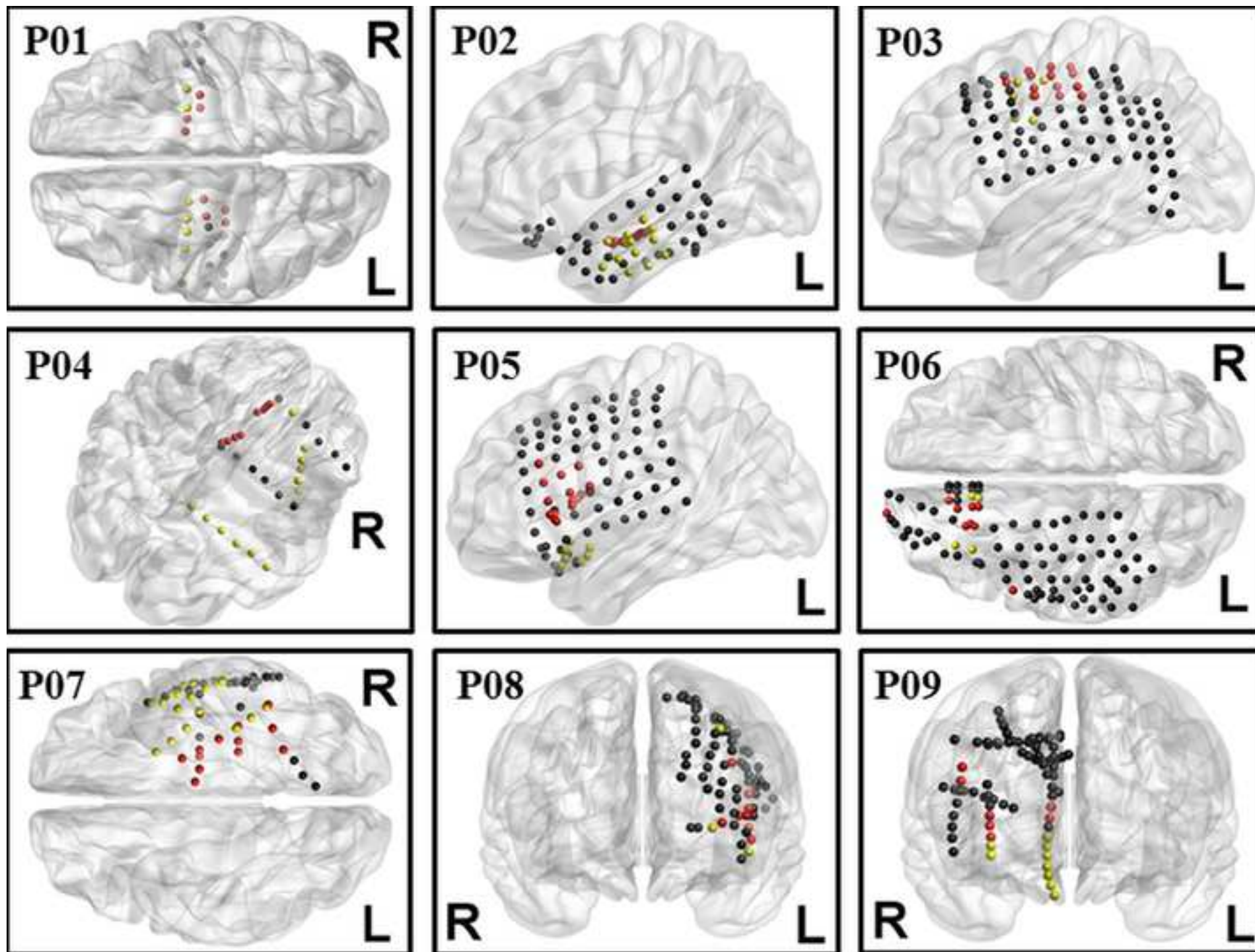
826 **Figure Legends**

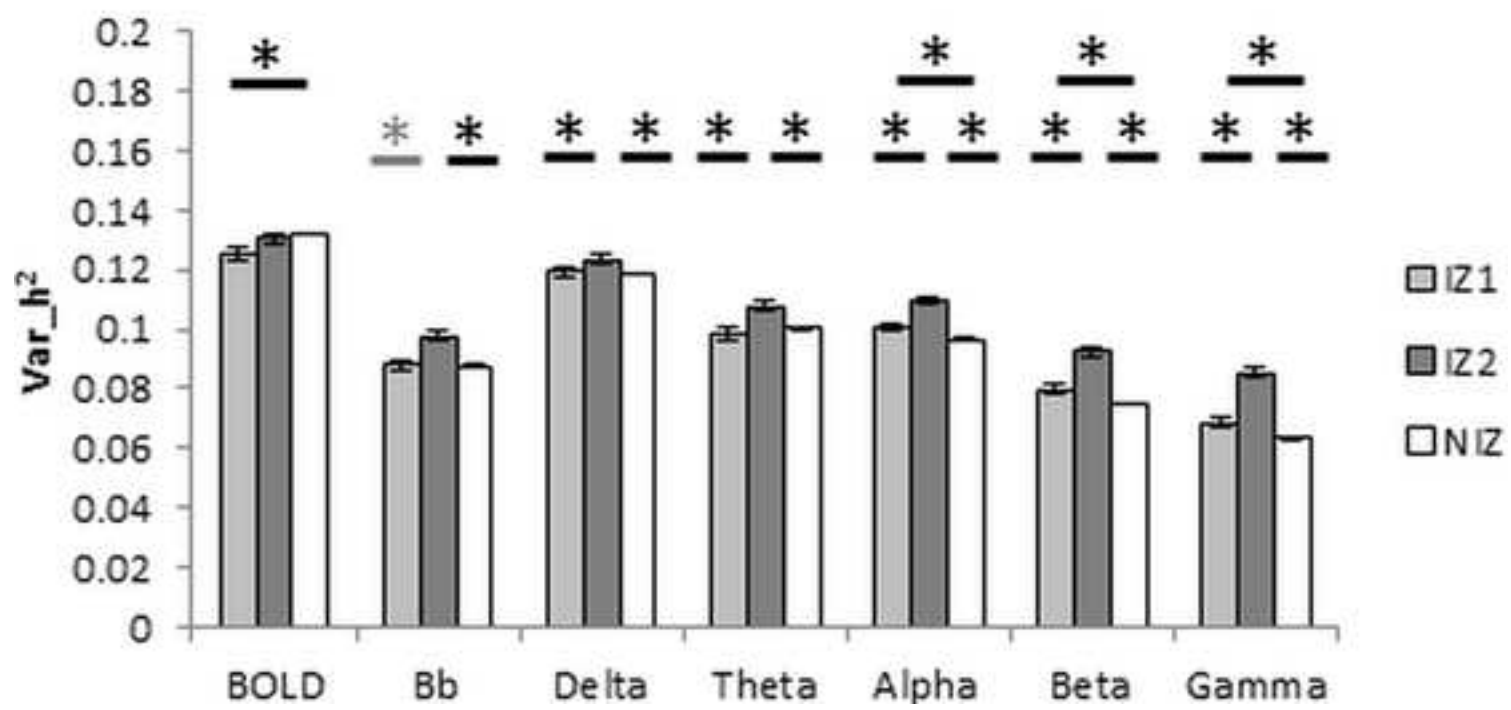
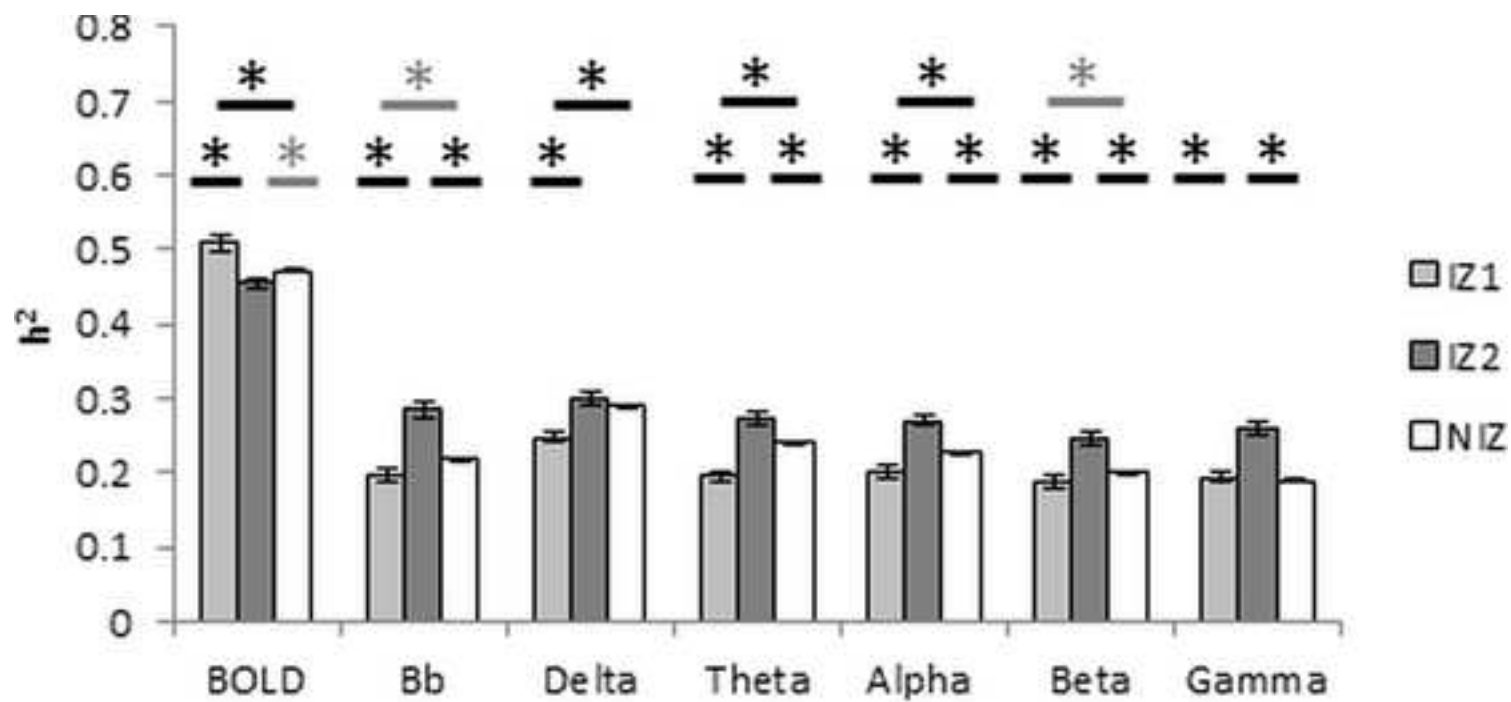
1  
2 827 **Fig.1 Regions of interest (ROIs)** Schematic representation of individual implantation schemes  
3  
4 828 projected onto templates in MNI space. Red spheres: ROIs in the primary irritative zone (IZ1); yellow  
5  
6 829 spheres: ROIs in secondary irritative zone (IZ2); black spheres: ROIs in non-involved zone (NIZ).  
7  
8  
9 830 Created using BrainNet Viewer (Xia et al. 2013)

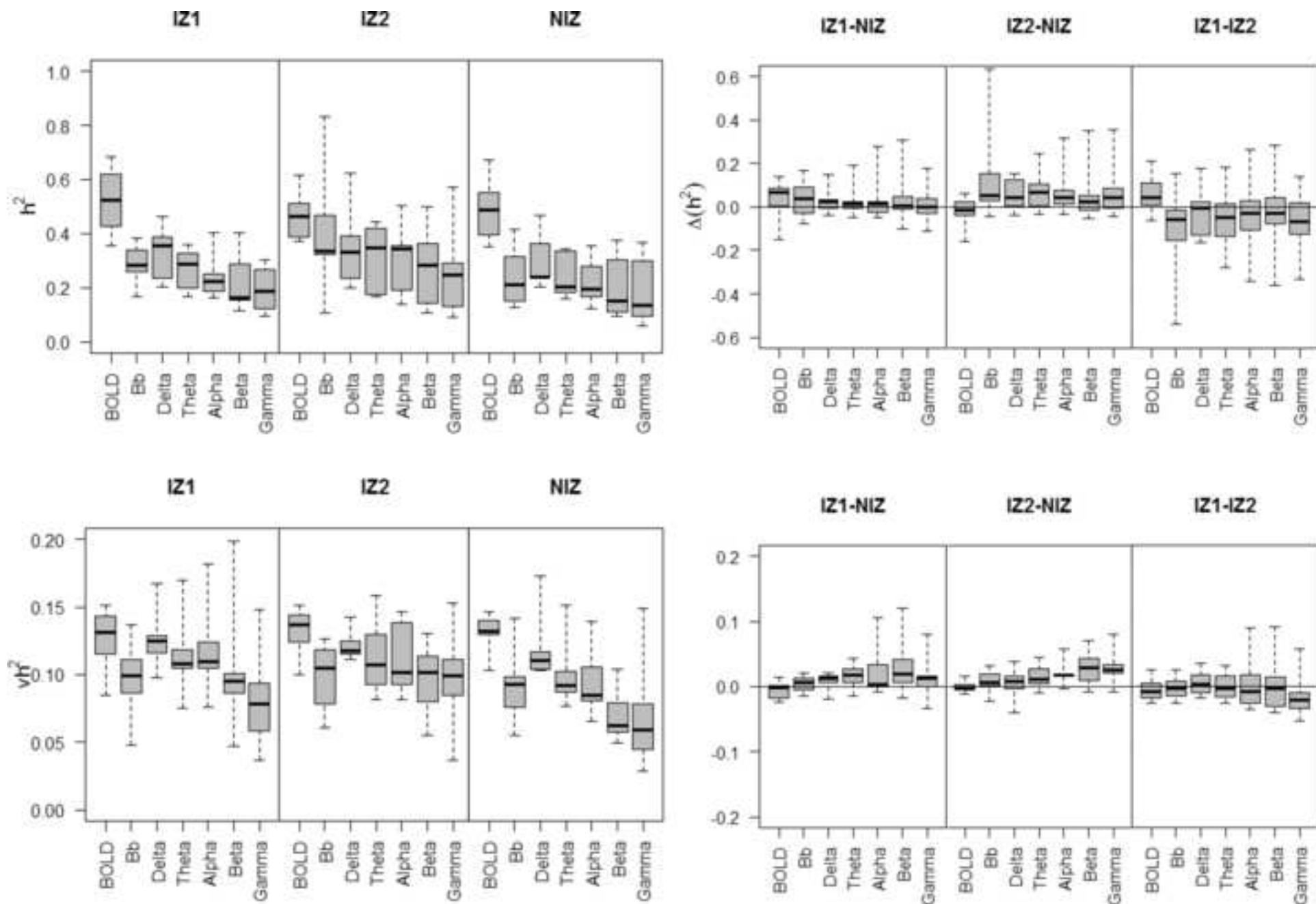
10  
11 831  
12  
13 832 **Fig.2 Post-hoc t-contrasts between zones in terms of functional connectivity (top) and variability**  
14  
15 833 **(bottom)** Values correspond to adjusted means accounting for covariates other than zone. Error bars  
16  
17 834 correspond to standard error of the mean. Bb, Broadband. Dark grey indicates a test significant at  
18  
19  
20 835  $p < 0.05$ , solid black indicates significance at a Bonferroni-corrected level of  $p < 0.007$ .

21  
22 836  
23  
24 837 **Fig.3 Inter-individual variability in connectivity metrics and inter-zone contrasts**  
25  
26 838 Boxplots of inter-individual variability in  $h^2$  (top) and  $vh^2$  (bottom). Inter-individual estimates in  
27  
28 839 mean (Left) estimates, and contrasts between zones (right). Note the distribution of data for the  
29  
30 840 contrast IZ1-NIZ around zero for  $\Delta h^2$  across modalities.

31  
32  
33 841  
34  
35 842  
36  
37  
38 843







## Tables

Patient	Sex	Age (yrs)	Hand	Diagnosis	Onset (yrs)	Seizure Frequency	MRI	Surgical Resection	Outcome	
									ILAE	Months
P01	M	26	Right	Bi-Temporal	7	Monthly	L. HS	L. TL	I	38
P02	F	31	Right	Temporal	6	Weekly	NL	L. TL	IV	43
P03	M	28	Right	Frontal	12	Daily	FCD L. SFG\ MFG	L. SFG/MFG Sup. SMA	I	22
P04	M	38	Right	Frontal	8	Daily	L HS*	R. SMA, m. SFG	I	23
P05	F	34	Right	Frontal	7	Daily	FCD L. IFG	L. SFG/MFG	I	19
P06	F	27	Left	Frontal	3	Daily	NL	L. SFG	I	24
P07	M	24	Right	Temporal	15	Weekly	NL	R. TL	IV	19
P08	M	34	Right	Frontal	9	Daily	FCD L. MFG	L. MFG/IFG	I	11
P09	M	32	Right	Frontal	16	Weekly	NL	R. OrbF/IFG	I	22

**Table 1: Patient Clinical Demography.** *Abbreviations:* yrs=years, Hand.=Handedness, M=male, F=female, R=right, L=left, NL=non-lesional, HS=hippocampal sclerosis, FCD=focal cortical dysplasia, SFG=superior frontal gyrus, MFG=middle frontal gyrus, IFG=inferior frontal gyrus, TL=temporal lobe, Sup.= superior, SMA= supplementary motor area, OrbF=orbitofrontal gyrus. *ILAE surgery outcome:* I: Completely seizure free, no aura; II: Only auras, no other seizures; III: One or two seizure days per years,  $\pm$  auras; IV: Four seizure days per year to 50% reduction of baseline seizure days,  $\pm$  auras; V: Less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days,  $\pm$  auras; VI: More than 100% increase of baseline seizure days,  $\pm$  auras. \*Hippocampal sclerosis was considered incidental in this patient. Ictal SPECT, PET, MEG and scalp EEG all support a right frontal seizure origin.

	Clinical Electrophysiological Zone					
	EZ/IZ1		IZ2		NIZ	
<b>Total No. of ROIs</b>	88		86		396	
<b>Total Pairwise Interactions</b>	410		478		10655	
	Grids	Depth	Grid	Depth	Grid	Depth
<b>P01</b>	0	8	0	8	0	14
<b>P02</b>	0	8	10	4	38	0
<b>P03</b>	13	0	0	6	43	12
<b>P04</b>	0	8	0	13	0	11
<b>P05</b>	8	7	8	0	54	4
<b>P06</b>	9	0	4	0	71	0
<b>P07</b>	6	6	20	0	19	6
<b>P08</b>	6	2	3	1	3	69
<b>P09</b>	0	7	0	9	0	52

**Table 2 – Regions of interest/electrodes.** Numbers of recording electrodes localized to each electrophysiological zone, overall (top) and for each participant (bottom). Pairwise interactions refers to functional connectivity estimates that contribute to the sample analysed at the group level, and include all possible interactions within each individual and each zone. Interactions between zones were not considered.

Metric	Modality	IZ1		IZ2		NIZ		
		BOLD $h^2$	BOLD $vh^2$	BOLD $h^2$	BOLD $vh^2$	BOLD $h^2$	BOLD $vh^2$	
$h^2$	icEEG Bband	r	-	-	-0.2	0.09	-	
		p	-	-	<.0001	<.0001	-	
	Delta icEEG	r	0.16	-	-	-0.15	0.19	-
		p	0.0008	-	-	0.001	<.0001	-
	Theta icEEG	r	-	-	-	-0.17	0.13	-
		p	-	-	-	0.0002	<.0001	-
	Alpha icEEG	r	-	-	-	-0.18	0.11	-
		p	-	-	-	<.0001	<.0001	-
	Beta icEEG	r	-	-	-	-0.23	0.1	-
		p	-	-	-	<.0001	<.0001	-
	Gamma icEEG	r	-	-	-	-0.27	0.05	-
		p	-	-	-	<.0001	<.0001	-
	$vh^2$	BOLD	r	-0.41		-0.26		-0.17
			p	<.0001		<.0001		<.0001
icEEG Bband		r	-	-	-	-	0.14	-
		p	-	-	-	-	<.0001	-
Delta icEEG		r	-	-	-	-	0.18	-
		p	-	-	-	-	<.0001	-
Theta icEEG		r	-	-	-	-	0.15	-
		p	-	-	-	-	<.0001	-
Alpha icEEG		r	-	-	-	0.15	0.13	0.06
		p	-	-	-	0.001	<.0001	<.0001
Beta icEEG		r	-	-	-	-	0.08	0.05
		p	-	-	-	-	<.0001	<.0001
Gamma icEEG		r	-	-	-	-	0.07	0.05
		p	-	-	-	-	<.0001	<.0001
IEDs	r	0.2	-	-	0.24	-	-	
	p	<.0001	-	-	<.0001	-	-	

**Table 3 – Inter-modal connectivity correlation (Pearson’s r) between connectivity metrics.**

Correlations considered significant at a Bonferroni-corrected level  $p < 0.002$ . Abbreviations: Bband, broadband; Mn, mean.



Metric	Modality	Whole Model (14)	Patient (8)	Mean IEDs (11531)	Euclid. Dist. (11531)	Elec. Type (2)	Zone (2)
$h^2$	<b>BOLD</b>	190.4	208.6	4.9	67.9	-	13.5
	<b>icEEG Bband</b>	453.5	265.2	-	812.2	378	47.9
	<b>Delta icEEG</b>	357.3	46.4	70.2	261.3	85.2	20.1
	<b>Theta icEEG</b>	219.5	44.1	21.8	421.1	123.2	40.5
	<b>Alpha icEEG</b>	164.7	57.67	-	262.3	165.2	33.81
	<b>Beta icEEG</b>	318.2	47.7	9.2	299	203.4	30.43
	<b>Gamma icEEG</b>	443.5	244.1	131.3	209.8	165.7	52.5
$vh^2$	<b>BOLD</b>	35.9	54.7	10,	7.6	-	3.9
	<b>icEEG Bband</b>	839.1	471.5	-	260.2	195.3	21.5
	<b>Delta icEEG</b>	437	194.5	16	113	96.4	4.2
	<b>Theta icEEG</b>	639.7	292.4	226.1	135.8	176.2	15.35
	<b>Alpha icEEG</b>	571.8	239	330.6	72.2	340.3	44.1
	<b>Beta icEEG</b>	739.3	161.8	792.3	218.6	401.9	88.3
	<b>Gamma icEEG</b>	1136.7	604.2	140.7	200.8	444.7	182.6

**Table 4. Significant main effects (F)** Numbers in brackets indicate degree of freedom. Significant to  $p < 0.007$ , non-significant effects indicated by a dash(-).

Metric	Modality		IZ1	IZ2	NIZ	
$h^2$	<b>BOLD</b>	<b>Mn</b>	0.51	0.45	0.47	
		<b>SD</b>	0.20	0.17	0.17	
	<b>icEEG Bband</b>	<b>Mn</b>	0.20	0.29	0.22	
		<b>SD</b>	0.20	0.23	0.17	
	<b>Delta icEEG</b>	<b>Mn</b>	0.25	0.30	0.29	
		<b>SD</b>	0.17	0.18	0.15	
	<b>Theta icEEG</b>	<b>Mn</b>	0.19	0.27	0.24	
		<b>SD</b>	0.16	0.17	0.14	
	<b>Alpha icEEG</b>	<b>Mn</b>	0.20	0.27	0.23	
		<b>SD</b>	0.15	0.16	0.13	
	<b>Beta icEEG</b>	<b>Mn</b>	0.19	0.25	0.20	
		<b>SD</b>	0.16	0.16	0.13	
	<b>Gamma icEEG</b>	<b>Mn</b>	0.19	0.26	0.19	
		<b>SD</b>	0.16	0.17	0.15	
	$vh^2$	<b>BOLD</b>	<b>Mn</b>	0.13	0.13	0.13
			<b>SD</b>	0.04	0.04	0.04
<b>icEEG Bband</b>		<b>Mn</b>	0.09	0.10	0.09	
		<b>SD</b>	0.04	0.03	0.04	
<b>Delta icEEG</b>		<b>Mn</b>	0.12	0.12	0.12	
		<b>SD</b>	0.03	0.03	0.04	
<b>Theta icEEG</b>		<b>Mn</b>	0.10	0.11	0.10	
		<b>SD</b>	0.03	0.03	0.03	
<b>Alpha icEEG</b>		<b>Mn</b>	0.10	0.11	0.10	
		<b>SD</b>	0.04	0.04	0.03	
<b>Beta icEEG</b>		<b>Mn</b>	0.08	0.09	0.07	
		<b>SD</b>	0.04	0.03	0.03	
<b>Gamma icEEG</b>		<b>Mn</b>	0.07	0.09	0.06	
		<b>SD</b>	0.04	0.04	0.03	

**Table 5**  $h^2$  and  $vh^2$  estimates by zone for each modality

	<b>Dependant Variable</b>	<b>IZ1-IZ2 (1)</b>	<b>IZ1-NIZ (1)</b>	<b>IZ2-NIZ (1)</b>
<b>h<sup>2</sup></b>	<b>BOLD</b>	25.4	16.8	4*
	<b>icEEG Broadband</b>	82	6.6*	70.9
	<b>Delta icEEG</b>	33.8	30.7	-
	<b>Theta icEEG</b>	80	40	20.4
	<b>Alpha icEEG</b>	64	11.3	40.2
	<b>Beta icEEG</b>	51.8	3.9*	45.5
	<b>Gamma icEEG</b>	58.9	-	100.9
<b>Var_h<sup>2</sup></b>	<b>BOLD</b>	-	7.7	-
	<b>icEEG Broadband</b>	25.8	-	40.7
	<b>Delta icEEG</b>	4.2*	-	8.3
	<b>Theta icEEG</b>	24.3	-	24.9
	<b>Alpha icEEG</b>	29.2	7.9	7.9
	<b>Beta icEEG</b>	60.8	14.4	176.6
	<b>Gamma icEEG</b>	146.6	19	364.5

**Table 6 - Significant post-hoc t-contrasts for Zone (F)** numbers in brackets indicate degree of freedom. Non-significant test marked with dash (-), significant at  $p < 0.05$  marked with asterix (\*), all others significant at bonferonni-corrected level of  $p < 0.007$ .



Click here to access/download  
**Supplementary Material**  
ridley et al\_SupplInfo.docx





Click here to access/download  
**Supplementary Material**  
SuppFig1.tif

