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

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connectivity correlation (IMCC). We quantified IMCC in 9 patients with drug-resistant epilepsy i) within brain networks in 'healthy' non-involved cortical zones (NIZ) and ii) within brain networks involved in generating seizures and interictal spikes (IZ1) or solely spikes (IZ2). Functional connectivity (h_2) estimates for 10 minutes of resting-state data were obtained between each pair of electrodes within each clinical zone for both icEEG and fMRI. A sliding window approach allowed us to quantify the variability over time of h_2 (vh_2) as an indicator of connectivity dynamics. We observe significant positive IMCC for h_2 and vh_2 , for multiple bands in the NIZ only, with the strongest effect in the lower icEEG frequencies. Similarly, intra-modal h_2 and vh_2 were found to be differently modified as a function of different epileptic processes: compared to NIZ, h_2 BOLD was higher in IZ1, but lower in IZ2, while h_2 icEEG showed the inverse pattern. This corroborates previous observations of inter-modal connectivity discrepancies in pathological cortices, while providing the first direct invasive and simultaneous comparison in humans. We also studied time-resolved FC variability multimodally for the first time, finding that IZ1 shows both elevated internal h_2 BOLD and less rich dynamical variability, suggesting that its chronic role in epileptogenesis may be linked to greater homogeneity in self-sustaining pathological oscillatory states.

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1 **Full Title:** *Simultaneous intracranial EEG-fMRI shows inter-modality correlation in time-resolved*
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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_{BOLD} was higher in IZ1, but lower in IZ2, while h^2_{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_{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.

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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
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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
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11 152 discrepancies are due to intersession effects, while the contrary case would implicate ‘genuine’
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13 153 differences in the signals being measured and/or their relationships. Extending this to time-resolved
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15 154 variability in FC, allows us to characterise the range of variability in normal regions, and whether the
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17 155 repertoire of functions states is impacted differentially by chronic exposure to different kinds of
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19 156 epileptic activity. Leveraging simultaneous icEEG-fMRI for the first time in the interictal resting
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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).

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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**.

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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 (≤ 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°), 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 μ 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*

Analyzer software (V1.3). Data was analysed after subtracting the common average reference (minimum number of electrodes included: 30, P01), and filtered according to several frequency ranges 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 (12.4-24 Hz); and Gamma (24-100 Hz).

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

2.4 Functional connectivity analysis

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

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

With

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

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

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

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_{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_{BOLD} was negatively correlated with vh^2_{BOLD} . A negative
335 association was also exhibited between vh^2_{BOLD} and vh^2_{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_{BOLD} and h^2_{icEEG} outside of the NIZ with the
338 exception of the delta band in IZ1. Similarly, the only relationship between vh^2_{icEEG} and vh^2_{BOLD} in
339 epileptic cortices was a positive correlation observed in the alpha band in IZ2. Finally, while negative
340 correlations between h^2_{BOLD} and vh^2_{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_{icEEG} and vh^2_{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_{BOLD} in IZ2, while correlating
346 with h^2_{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_{BOLD} , and IZ2 lower h^2_{BOLD} compared to NIZ, while for h^2_{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_{icEEG} and reduced h^2_{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_{icEEG} , and lower vh^2_{BOLD} .

361 4. DISCUSSION

1 362 The current work confirms a previously observed discrepancy between icEEG- and BOLD-
2 derived FC findings (h^2) (Bettus et al. 2008; Bettus et al. 2011) and extends it to FC variability over
3 363 time (vh^2); in addition, we shed new light on the differential impact of different epileptic processes.
4
5 364 We demonstrate for the first time using simultaneously acquired icEEG-fMRI that epileptic cortices
6
7 365 are distinguished by their internal multimodal resting-state FC as a function of their involvement in
8
9 366 different, clinically-relevant epileptic processes. Furthermore, we provide the first evidence that the
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11 367 inter-modal connectivity correlation that exists in unaffected regions may be modified in cortices
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13 368 affected by epileptic pathology, when estimating h^2 and vh^2 in unaffected regions and using invasive
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15 369 and simultaneous electrophysiological and haemodynamic signals.
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18 372 4.1 Inter-modal connectivity correlation in physiological and pathological cortices

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20 373 The non-invasive BOLD signal is an indirect measure of neurological activity, motivating
21
22 374 interest in better understanding its electrophysiological correlates, including in terms of icEEG-
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24 375 derived connectivity and its relationship to both spontaneous BOLD activity and resting-state
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26 376 functional connectivity. Correlates from electrophysiological activity (as opposed to connectivity) at
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28 377 multiple spatial and temporal scales have been proposed (Keilholz 2014; Tagliazucchi and Laufs
29
30 378 2015), with both high-frequency local field potentials (Shmuel and Leopold 2008; Nir et al. 2008;
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32 379 Schölvinck et al. 2010), and lower frequencies (Lu et al. 2007; He et al. 2008; Pan et al. 2013; Lu et
33
34 380 al. 2016) being advanced as electrophysiological correlates of spontaneous rsfMRI fluctuations.
35
36 381 Others have examined the extent to which connectivity estimates derived from EEG and BOLD are
37
38 382 associated with one another, in terms of the intermodal correlation of the connectivity estimates
39
40 383 derived from each modality. Invasive electrophysiological recordings in rats indicate relationships
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42 384 between BOLD correlations and EEG band power correlations that are strongest in lower frequency
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44 385 bands, especially delta, but extending to gamma (Lu et al. 2007; Pan et al. 2011). Modulation by
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46 386 exogenous stimulation of rsfMRI functional connectivity in rat whisker barrel cortex has been found
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48 387 to be reflected in the delta range, but not at higher frequencies (Lu et al. 2016). In humans, it has been
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50 388 shown that BOLD covariance (functional connectivity) matrices can be well explained based on EEG
51
52 389 covariance matrices - similarly so across bands - while the reverse is only true in the lower frequency
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54 390 bands (Deligianni et al. 2014). Here, in the first study to combine invasive electrophysiological
55
56 391 recording and simultaneous fMRI acquisition, we observe correlations between FC estimated on
57
58 392 haemodynamic and electrophysiological signals across frequency bands in non-involved, 'healthy'
59
60 393 cortex (**Table 3**). We find the strongest relationships at lower frequencies, possibly reflecting a bias
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62 394 toward lower bands in maintaining relationships over distant regions due to the relationship between
63
64 395 distance and signal delay (Schölvinck et al. 2013).
65

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_{BOLD} connectivity leading to its reduction in IZ2 (**Figure 2, top**) and greater variability as measured by vh^2_{icEEG} (**Figure 2, bottom and Table 2**), versus the positive correlation observed between IEDs and vh^2_{BOLD} and the anti-correlation of vh^2_{BOLD} and h^2_{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
1 467 (Harris et al. 2013). This is suggestive of a broad comparability between spontaneous and evoked
2
3 468 neurovascular coupling which may be subject to modification in the context of epilepsy.
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5 469 Our results suggest that multimodal differences persist despite an equivalent *incidence* of
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7 470 inter-modal between-session factors (as ensured by simultaneous acquisition), though this in itself
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9 471 does not exclude a difference in *impact* between modalities. Modelling may be one means of
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11 472 understanding how such differences contribute to the discrepancies seen here, but it should be noted
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13 473 that the choice of parameters derived from one signal for the understating of another is highly non-
14
15 474 trivial. For example, an argument for a disruptive effect of interictal epileptic transients such as IEDs
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17 475 on connectivity has a *prima facie* plausibility. However, empirical results have been more equivocal
18
19 476 with negative (Nissen et al. 2016), positive (Bartolomei et al. 2013a) and null (Bettus et al. 2008)
20
21 477 associations of IEDs with FC in epileptics networks observed in scalp and invasive electrophysiology,
22
23 478 but also overall limited-to-no-effect of removing IED-containing epochs by censoring data (Bettus et
24
25 479 al. 2008; Warren et al. 2010b; Bartolomei et al. 2013a). On the other hand, general linear modelling of
26
27 480 IEDs and other epileptic transient provided some of the earliest evidence of an interaction of epilepsy
28
29 481 with resting-state phenomena in the form of IED- and seizure-associated BOLD changes in regions
30
31 482 associated with intrinsic connectivity networks, most especially the default mode network (Gotman
32
33 483 and Pittau 2011; van Graan et al. 2015). Interictal phenomena may be associated with increases,
34
35 484 decreases or unchanged BOLD signal (Béнар et al., 2006; Salek-Haddadi et al., 2006; Stefan and
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37 485 Lopes da Silva, 2013; Thornton et al., 2011), and BOLD changes may be found in regions with no
38
39 486 apparent involvement on EEG (Kobayashi et al. 2006). Interpreting the variability of these results is
40
41 487 further complicated by recent evidence that coupling is state- and time-dependant in addition to being
42
43 488 spatially organized in the resting-state (Feige et al. 2016). While suggestive of a framework for
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45 489 understanding the differential impact between modalities, how altered coupling might pertain to the
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47 490 findings in the current study - the focus of which is FC in epileptic networks rather than resting
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49 491 activity in ICNs per se - is unclear. Indeed, there is evidence of dissociation between different means
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51 492 of characterizing resting state activity in epilepsy, with discordant finding in terms of the amplitude
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53 493 and connectivity of resting state activity in the same patients (Zhang et al. 2015). As noted above,
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55 494 multiple processes that contribute to neurovascular coupling and hence the BOLD-signal generation
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57 495 cascade are effected in epilepsy, and as such represent sources of unmodeled noise standing between
58
59 496 underlying processes and the signals as estimated via such metrics as (de-)activation or connectivity.
60
61 497 The separate contributions of perfusion deficits (Duncan 2009) and altered metabolic demands in the
62
63 498 chronic epileptic state and under the specific influence of epileptic transients will likely need to be
64
65 499 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_{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_{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_{BOLD} and a reduction in vh^2_{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_{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_{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
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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
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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
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9 592 subject to epileptic processes, with a confirmation of inter-modality discrepancies in functional
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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.

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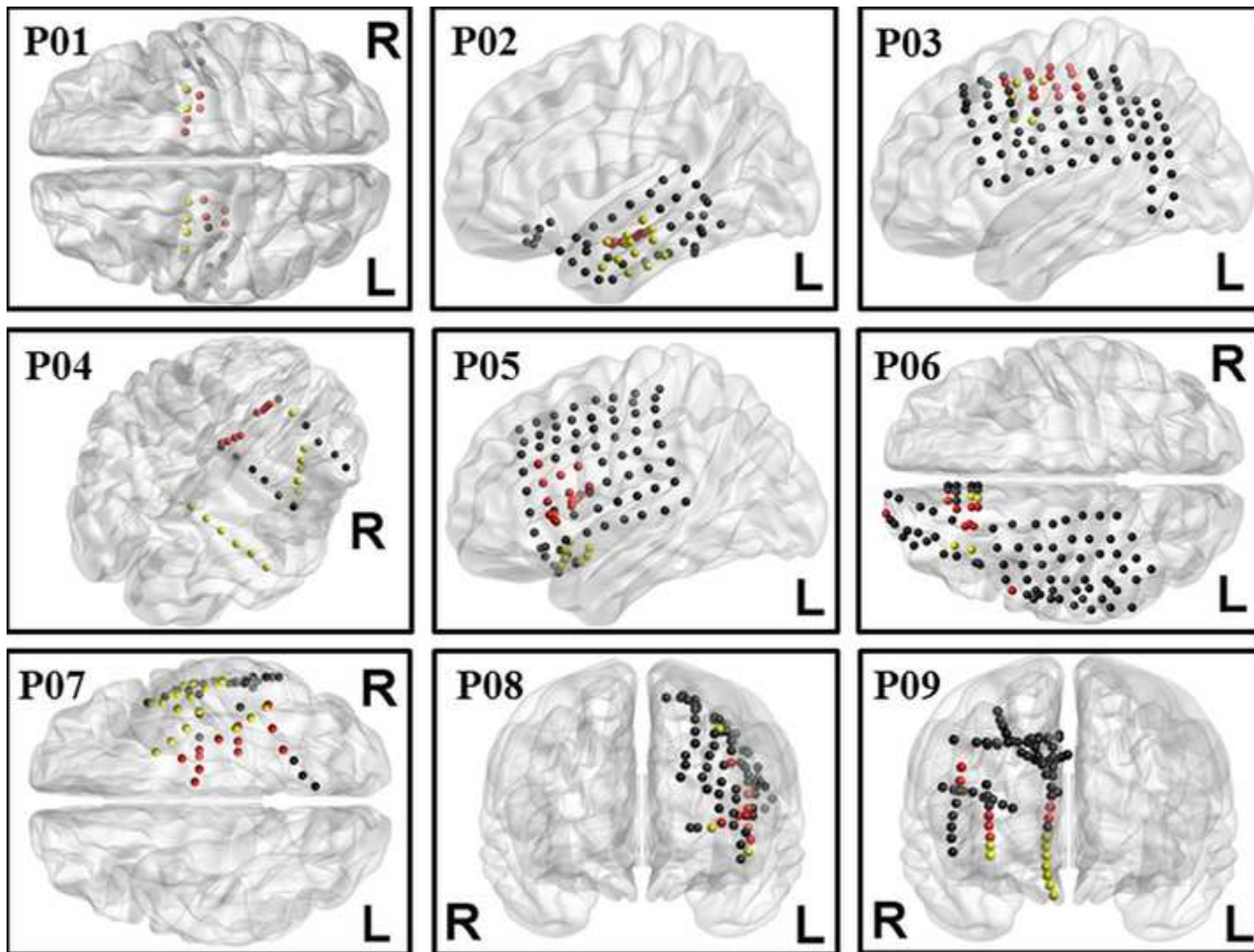
826 **Figure Legends**

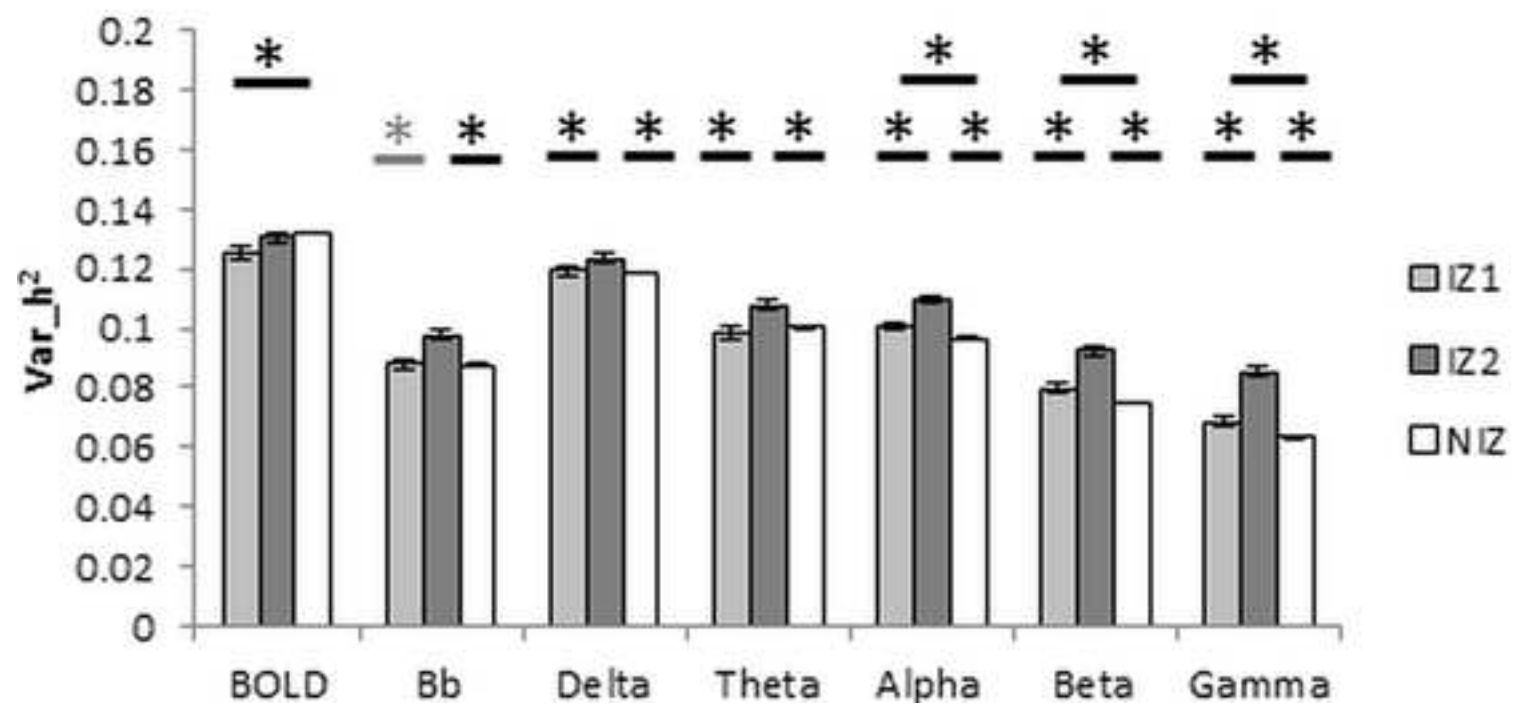
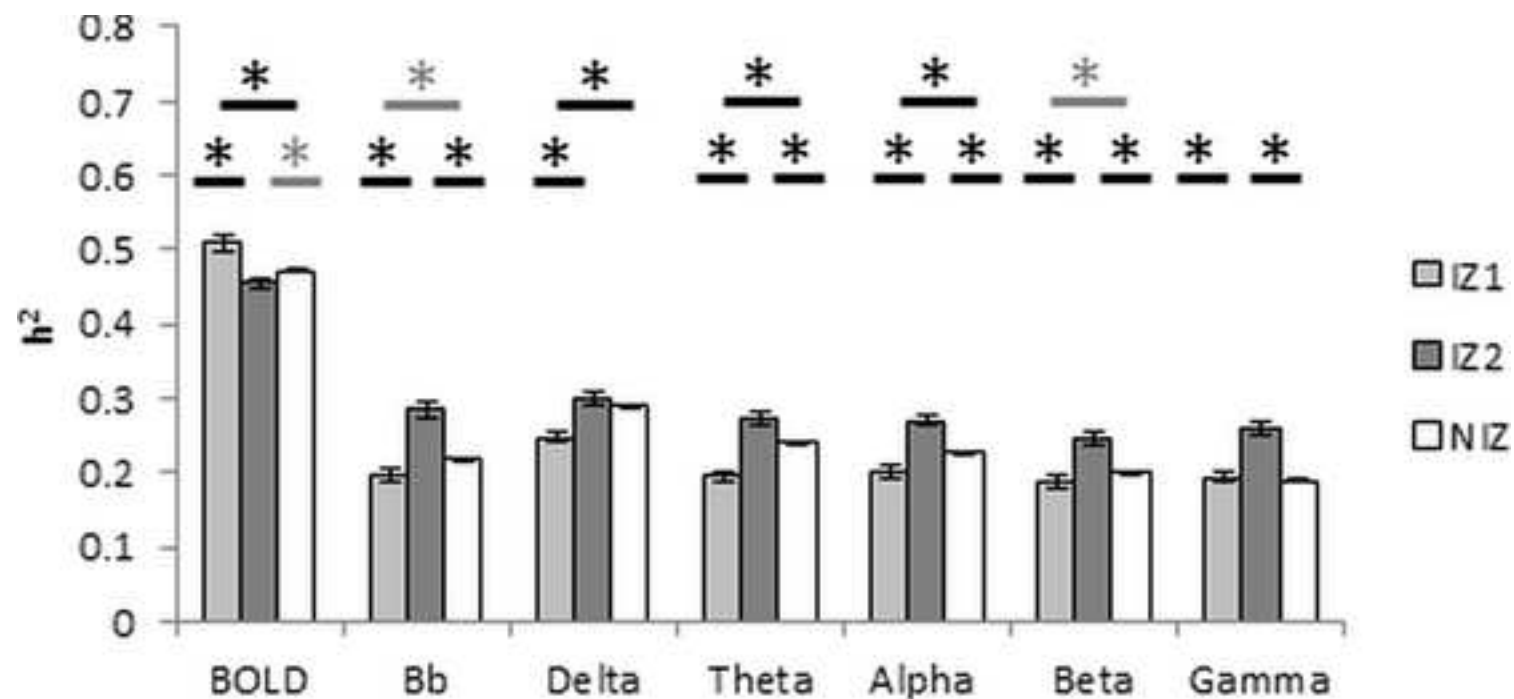
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2 827 **Fig.1 Regions of interest (ROIs)** Schematic representation of individual implantation schemes
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4 828 projected onto templates in MNI space. Red spheres: ROIs in the primary irritative zone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

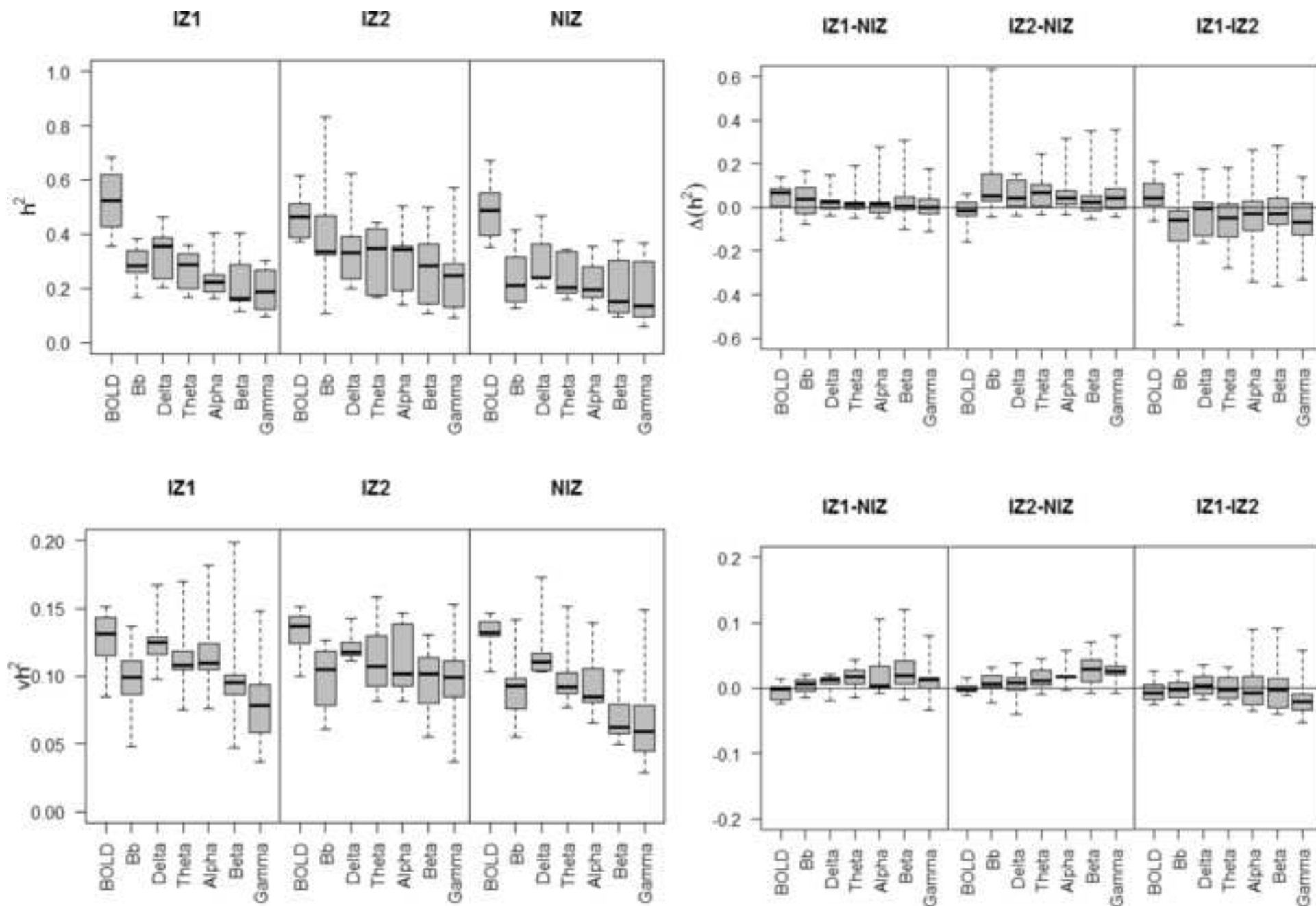
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13 832 **Fig.2 Post-hoc t-contrasts between zones in terms of functional connectivity (top) and variability**
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15 833 **(bottom)** Values correspond to adjusted means accounting for covariates other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

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

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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/IF G	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	
Total No. of ROIs	88		86		396	
Total Pairwise Interactions	410		478		10655	
	Grids	Depth	Grid	Depth	Grid	Depth
P01	0	8	0	8	0	14
P02	0	8	10	4	38	0
P03	13	0	0	6	43	12
P04	0	8	0	13	0	11
P05	8	7	8	0	54	4
P06	9	0	4	0	71	0
P07	6	6	20	0	19	6
P08	6	2	3	1	3	69
P09	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	BOLD	190.4	208.6	4.9	67.9	-	13.5
	icEEG Bband	453.5	265.2	-	812.2	378	47.9
	Delta icEEG	357.3	46.4	70.2	261.3	85.2	20.1
	Theta icEEG	219.5	44.1	21.8	421.1	123.2	40.5
	Alpha icEEG	164.7	57.67	-	262.3	165.2	33.81
	Beta icEEG	318.2	47.7	9.2	299	203.4	30.43
	Gamma icEEG	443.5	244.1	131.3	209.8	165.7	52.5
vh^2	BOLD	35.9	54.7	10,	7.6	-	3.9
	icEEG Bband	839.1	471.5	-	260.2	195.3	21.5
	Delta icEEG	437	194.5	16	113	96.4	4.2
	Theta icEEG	639.7	292.4	226.1	135.8	176.2	15.35
	Alpha icEEG	571.8	239	330.6	72.2	340.3	44.1
	Beta icEEG	739.3	161.8	792.3	218.6	401.9	88.3
	Gamma icEEG	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	BOLD	Mn	0.51	0.45	0.47	
		SD	0.20	0.17	0.17	
	icEEG Bband	Mn	0.20	0.29	0.22	
		SD	0.20	0.23	0.17	
	Delta icEEG	Mn	0.25	0.30	0.29	
		SD	0.17	0.18	0.15	
	Theta icEEG	Mn	0.19	0.27	0.24	
		SD	0.16	0.17	0.14	
	Alpha icEEG	Mn	0.20	0.27	0.23	
		SD	0.15	0.16	0.13	
	Beta icEEG	Mn	0.19	0.25	0.20	
		SD	0.16	0.16	0.13	
	Gamma icEEG	Mn	0.19	0.26	0.19	
		SD	0.16	0.17	0.15	
	vh^2	BOLD	Mn	0.13	0.13	0.13
			SD	0.04	0.04	0.04
icEEG Bband		Mn	0.09	0.10	0.09	
		SD	0.04	0.03	0.04	
Delta icEEG		Mn	0.12	0.12	0.12	
		SD	0.03	0.03	0.04	
Theta icEEG		Mn	0.10	0.11	0.10	
		SD	0.03	0.03	0.03	
Alpha icEEG		Mn	0.10	0.11	0.10	
		SD	0.04	0.04	0.03	
Beta icEEG		Mn	0.08	0.09	0.07	
		SD	0.04	0.03	0.03	
Gamma icEEG		Mn	0.07	0.09	0.06	
		SD	0.04	0.04	0.03	

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

	Dependant Variable	IZ1-IZ2 (1)	IZ1-NIZ (1)	IZ2-NIZ (1)
h²	BOLD	25.4	16.8	4*
	icEEG Broadband	82	6.6*	70.9
	Delta icEEG	33.8	30.7	-
	Theta icEEG	80	40	20.4
	Alpha icEEG	64	11.3	40.2
	Beta icEEG	51.8	3.9*	45.5
	Gamma icEEG	58.9	-	100.9
Var_h²	BOLD	-	7.7	-
	icEEG Broadband	25.8	-	40.7
	Delta icEEG	4.2*	-	8.3
	Theta icEEG	24.3	-	24.9
	Alpha icEEG	29.2	7.9	7.9
	Beta icEEG	60.8	14.4	176.6
	Gamma icEEG	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 $p < 0.007$.



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