Resting-state EEG-correlated fMRI
Why, how and what

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Objectives of this presentation

• Provide guidelines for choosing synchronous multi-modal acquisitions

• Describe EEG-fMRI methodology
  – Insure adequate EEG and image data quality
  – Data analysis strategies

• Illustrate applications in Epilepsy
  – Mapping in Epilepsy
  – Networks in Epilepsy
  – Fast signal changes
Models of brain activity have many *observables*:

- Electrical
- Magnetic
- Chemical
- Vascular
- Optical
- NMR
- etc.

Understanding their *interdependence* is key

*What happens to parameter Y when parameter X changes?*

Space science analogy:

*“Pack the Mars lander with as many instruments as possible”*
EEG & fMRI

**EEG**
- Important observable of brain activity in humans
- Reflects neuronal signal generation and synchronisation
- Important clinical tool in epilepsy (*epileptic spikes*, seizures, etc)
- Non-invasive (scalp) & cheap
- Limitations in localisation

**fMRI**
- Allows tomographic visualisation of haemodynamic changes associated with changes in brain activity
- Has better temporal resolution than PET (…for epileptic spikes)
- Has poorer temporal resolution than EEG
- Is non-invasive (BOLD)
BOLD: Blood Oxygenation Level-Dependent effect

- fMRI acquisition is sensitive to local differences in magnetic susceptibility (an intrinsic property of any material)
- Deoxyhemoglobin and oxyhemoglobin have different susceptibilities

Increased neuronal activity

Increased metabolic rate

Increased volume

Increased blood flow - Oxygen level exceeds metabolic demand

Decreased deoxy-Hb / oxy-Hb

Increased MR signal
BOLD FMRI

Effect of blood flow increase

Resting cortex

Activated cortex

arteriole

venule

capillary bed

Deoxy-Hb

Oxy-Hb
BOLD FMRI
Hemodynamic response function

The SPM2 Canonical Haemodynamic Response Function (HRF)
fMRI: Processing and analysis

**SPM software**: data pipeline

- Time-series data
- Kernel
- Design matrix
- Statistical parametric map

- Realignement
- Smoothing
- General linear model
- Statistical inference

- Normalisation
- Template
- Parameter estimates

- Gaussian field theory

$p < 0.05$

*Taken from SPM course notes, UCL*
Synchrony of multi-modal acquisitions

1. Different sessions
   Fusion: comparison of averaged effects

2. Simultaneous
   Fusion: comparison of individual events

3. Interleaved
   – Special case of 2, when time scales allow (e.g. brief events followed by BOLD response, EEG patterns with long time scales)
The **need** for synchronous acquisitions

Principle: guarantee comparability of data across modalities

Criteria: brain state and effects of interest

1. Reproducible and predictable brain state
   - Different sessions
   - Study: averaged / typical effects only

2. Unpredictable, irreproducible or unique brain state:
   - Simultaneous (synchronous) acquisitions
   - Study: individual events – trial-by-trial
   - or averaged / typical effects
EEG-correlated fMRI: ‘EEG-fMRI’

**EEG used to define event onsets**

**EEG-fMRI in Epilepsy:**

- The aims of such studies are:
  - Demonstrate BOLD changes associated with epileptiform discharges
  - Localise the generators of epileptiform discharges
  - Improve our understanding of the underlying mechanisms of generation of epileptiform discharges

**EEG-fMRI of normal rhythms**

**EP-fMRI**
Averaged vs. trial-by-trial: The neuronal basis for BOLD decreases

[Shmuel et al, 2006]
fMRI:
Basic design and analytical principles

Standard (paradigm-based) fMRI

• Acquire two types of scans
  – Brain state 1 vs state 2 (e.g. active vs. rest)

• Perform t-test at each voxel
  – Scans 2 vs. scans 1

• Apply statistical threshold

• Present result as activation map
Unpredictable activity: Epilepsy
EEG-fMRI Methodology: problems and solutions

- **Patient safety:**
  - Risk of RF burning @ 1.5T and 3T
    - Use of current-limiting resistors
    - Use transmit head coil

- **Image quality:**
  - Signal loss due field perturbation around (metallic) electrodes
  - RF shielding
  - RF interference due to presence of electronic EEG equipment
    - Choice of component materials and RF shielding

- **EEG quality:**
  - Pulse & imaging artifact removal
Safety: Electrodes and leads

Mechanism: Induced currents in loop

(EEG lead-EEG electrode-patient-EEG electrodes-EEG lead-EEG amp)

Health risks:
- Very low frequency: Ulcers
- 1kHz: Stimulation
- RF: ‘RF burning’

Safety guidelines:
- Body temperature elevation
- Contact current (through conductor in contact with body)

[Lemieux et al, 1997]
Image quality: passive components

Mechanisms:

• $B_0$ perturbation due component ferro / para-magnetism
• RF perturbation (shielding) due presence of (numerous) electrodes

[Ag/AgCl electrodes]

[Au electrodes]

[K. Krakow et al., 1998]
Image quality: Effect of passive EEG components

Local effect of electrodes

Global effect on SNR_t

<table>
<thead>
<tr>
<th>B_0 (Tesla)</th>
<th>No cap mean ± SD</th>
<th>32 electrode cap mean ± SD</th>
<th>% Change</th>
<th>64 electrode cap mean ± SD</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>0.0166 ± 0.0007</td>
<td>0.0214 ± 0.0005</td>
<td>27 ± 8</td>
<td>0.0225 ± 0.0004</td>
<td>26 ± 10</td>
</tr>
<tr>
<td>3.0</td>
<td>0.0097 ± 0.0001</td>
<td>0.0102 ± 0.0004</td>
<td>4 ± 4</td>
<td>0.0106 ± 0.0002</td>
<td>15 ± 5</td>
</tr>
<tr>
<td>7.0</td>
<td>0.0076 ± 0.0003</td>
<td>0.0089 ± 0.0002</td>
<td>18 ± 4</td>
<td>0.0097 ± 0.0007</td>
<td>28 ± 13</td>
</tr>
</tbody>
</table>

32-channel cap @ 3T

[Mullinger et al, 2007]
Image quality:
Effect of active components

Artefact source:

• RF radiation from EEG recording electronics
• Can overlap with imaging bandwidth
• Usually in the form of regular pattern

Tests:

• Phantom (flip angle = 0)
• Inspection of background
Image quality:
Effect of active EEG components

<table>
<thead>
<tr>
<th>No amplifier</th>
<th>With amplifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF noise test</td>
<td></td>
</tr>
<tr>
<td>EPI image</td>
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</tbody>
</table>
EEG Quality

Two main problems:

- Image acquisition artefact
- Cardiac pulse artefact

Two main strategies:

- Avoid and/or minimize at source
- Software correction methods

NOT a formal comparison of published methods
EEG quality: pulse artefact

- (Sometimes called *ballistocardiogram*)
- Can mask spikes and distort ERP’s
  - Can be correlated to task (ERP)
- Present in most subjects but spatial distribution highly variable across subjects
  - Stronger anteriorly [Allen]
- Origin:
  1. Micro motion of body ($B_0$)/electrodes/wires due to heart beat
  2. Blood flow (‘Hall effect’)?

![Intra-MRI EEG](image)

50 uV 1 sec. LF= 0.12 Hz HF= 30 Hz
Pulse artefact reduction: main approaches

- Mechanical
  - Head vacuum cushion [Benar et al]
  - Wire immobilisation

- Recording
  - Bipolar montage to limit loop area [Goldman et al]

- Running average artefact subtraction
- Adaptive filtering
- Temporal PCA/ICA
Pulse artifact reduction: running average subtraction

Misconception: does not account at all for timing/morphological variability

[Allen et al., Neuroimage 1998]
Running average subtraction

No pulse artifact subtraction

- Fp2-F4
- F4-C4
- C4-P4
- P4-O2
- Fp1-F3
- F3-C3
- C3-P3
- P3-O1
- ECG

With pulse artifact subtraction

- Fp2-F4
- F4-C4
- C4-P4
- P4-O2
- Fp1-F3
- F3-C3
- C3-P3
- P3-O1
- ECG

50 μV
1 sec.
LF = 0.12 Hz HF = 30 Hz

[Allen et al., Neuroimage 1998]
Spike-triggered fMRI

25 uV

- Fp2-F8
- F8-T4
- T4-T6
- T6-O2
- Fp1-F7
- F7-T3
- T3-T5
- T5-O1
- ECG1-ECG2

1 sec.
### Pulse artefact correction methods: Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanical</strong></td>
<td>- Head vacuum cushion</td>
</tr>
<tr>
<td></td>
<td>- Wire immobilisation</td>
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<tr>
<td><strong>Recording</strong></td>
<td>- Bipolar montage to limit loop area [Goldman et al]</td>
</tr>
<tr>
<td><strong>(Running) average artefact subtraction</strong></td>
<td>[Allen, Goldman]</td>
</tr>
<tr>
<td></td>
<td>- Requires time marker (ECG)</td>
</tr>
<tr>
<td></td>
<td>- Issue: stationarity</td>
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<tr>
<td></td>
<td>- Real time possible</td>
</tr>
<tr>
<td></td>
<td>- Enhancements: Wavelet denoising [Kim]</td>
</tr>
<tr>
<td><strong>Adaptive filtering</strong></td>
<td>[Bonmassar, In]</td>
</tr>
<tr>
<td></td>
<td>- Requires time marker (ECG, EOG) OR motion sensor</td>
</tr>
<tr>
<td></td>
<td>- Real time possible</td>
</tr>
<tr>
<td><strong>(Temporal) SDV/PCA/ICA</strong></td>
<td>[Benar, Niazy, Otzenberg, Srivastava, Nakamura, Briselli]</td>
</tr>
<tr>
<td></td>
<td>- No need for time markers</td>
</tr>
<tr>
<td></td>
<td>- No assumption of stationarity</td>
</tr>
<tr>
<td></td>
<td>- Issue: component selection (stochastic behaviour of solution)</td>
</tr>
<tr>
<td></td>
<td>- Real-time implementation?</td>
</tr>
</tbody>
</table>
Continuous EEG-fMRI

Fp1-Pz
F7 – Pz
T3 – Pz
T5 – Pz
O1 – Pz
Fp2 – Pz
F8 – Pz
T4 – Pz
T6 – Pz
O2 – Pz
Fp1 – F7
F7 – T3
T3 – T5
T5 – O1
Fp2 – F8
F8 – T4
T4 – T6
T6 – O2
ECG

50uV

1 Second

LF = 0.5 Hz HF = 45 Hz
Continuous EEG-fMRI

Extra technical hurdle:

The image acquisition artifact

- Obliterates the EEG
- Origin: mainly gradient switching
- Much larger than EEG (100 x)
- EEG and scanning frequency bands overlap

[Anami, 2003]
Avoiding or limiting imaging artefact in EEG

- Mechanical means
  - All equipment secure
- Interleaved (periodic) EEG-fMRI
  - Periodic fMRI scanning with breaks to visualise EEG
  - Useful for the study of:
    - Prolonged spontaneous EEG events:
      - Sleep patterns, Seizures
    - Controlled events / patterns:
      - Modulated EEG (Alpha) [Goldman et al., 2002]
      - Evoked responses [Kruggel et al., 2001; Bonmassar et al., 2002]

* Imposes limits on EEG events that can be studied

- Stepping Stone acquisition scheme [Anami et al., 2003]
EEG system to perform continuous EEG-fMRI in epilepsy

• EEG recording system:
  – Dynamic range: 33mv, resolution 2μV
  – Sampling: 5kHz

• Acquire scanner slice acquisition pulse

• Calculate and subtract averaged artifact, synchronised to each MRI slice (or volume) acquisition

• Filtering (50Hz) and down-sampling

• Adaptive noise cancellation to reduce residual

[Allen et al., 2000]
Continuous EEG Correlated fMRI

Fp1-Pz
F7 – Pz
T3 – Pz
T5 – Pz
O1 – Pz
Fp2 – Pz
F8 – Pz
T4 – Pz
T6 – Pz
O2 – Pz
Fp1 – F7
F7 – T3
T3 – T5
T5 – O1
Fp2 – F8
F8 – T4
T4 – T6
T6 – O2
ECG
OSC

1 Second LF = 0.5 Hz HF = 45 Hz
50uV
Continuous EEG Correlated fMRI

Fp1-Pz  F7 – Pz  T3 – Pz  T5 – Pz  O1 – Pz  Fp2 – Pz  F8 – Pz  T4 – Pz  T6 – Pz  O2 – Pz  Fp1 – F7  F7 – T3  T3 – T5  T5 – O1  Fp2 – F8  F8 – T4  T4 – T6  T6 – O2  ECG  OSC

1 Second

50uV

LF = 0.5 Hz  HF = 45 Hz
Continuous EEG Correlated fMRI
Averaged imaging artifact subtraction: Results

• Median artifact:
  – Raw EEG: 4000 μV
  – Final: 8 μV

• Spectral Analysis:
  – 10-18% difference (outside vs. scanning)

• Spike identification
  – Raw EEG: 3% correct
  – Corrected EEG: 90% correct
Averaged artefact subtraction improvement: clock synchronisation

Problem: averaged artefact subtraction limited by EEG sampling rate
Principle: EEG digitization and MR acquisition synchronised through hardware link

Idea of M Cohen [HBM, 2001]

[Mendelkow, 2006]
Ritter et al’s comparative study

Visual stimulation paradigm
All data from interleaved EEG-fMRI

5 variants of the Allen method
1 new local implementation
• with interpolation
2 versions of Brain Vision Analyzer
• with / w/o template drift
2 versions of FASTR (Allen + Niazy)
• With / w/o limit on OBS over-fitting

➢ Very little difference in performance between latest versions
➢ FASTR tends to attenuate a bit more
➢ Old version of BV Analyzer: strong effects at high frequencies

[Ritter et al., MRI, 2007]
Image acquisition artifact removal: other approaches

• Fourier filtering
  [Hoffmann et al, 2000]

• PCA with gradient pulse
  [Logothetis et al., 2001]

• Acquire artefact model, match scale and subtract
  [Gareffa et al., 2003]
Artefact reduction performance assessment

- **Must assess artefact reduction and feature preservation**
- **Spectral power**
  - Normalised power spectrum ratio:
    \[
    \text{INPS} = \frac{\sum_{i=1}^{N} P_i^{\text{before}}}{\sum_{i=1}^{N} P_i^{\text{after}}}
    \]
- **Event of interest identification**
  - Epileptiform discharges (spikes,
- **Event of interest characteristic**
  - EP latency, amplitude
- **Source localisation / EEG field topography**
- fMRI results

Between conditions: $B_0 = \neq 0$
scanning ON/OFF
Scanner static field ($B_0$) strength effects

Pulse artefact: $\sim B_0$

Image quality
- Passive components: $\sim B_0$
- Active components: frequency band specific
- RF shielding from cap(?)

High field (>3T)
- Safety issues [Angelone et al.]
- Image quality
  - “Ink cap” [Vassios et al, 2007]
  - Electrode compatibility [Stevens et al, 2007]
- EEG quality
  - Pulse artefact [Bowtell, HBM 2006]
Methodology: Conclusions

• Need to consider carefully synchronicity requirements of experiment
• Data degradation always an issue in simultaneous-continuous experiments
• Interleaved acquisitions suitable for ERP’s
• Continuing developments in EEG artefact correction: pulse artefact
• Standard evaluation protocol lacking
• Continuous EEG-fMRI emerging as an important tool for the study of spontaneous brain activity
Aims of EEG-fMRI in Epilepsy

- Characterise the epileptogenic network (‘focus’)
  - Localisation
  - Syndrome classification
  - Haemodynamics
    - time course of change
    - network

- Map BOLD correlates of focal spikes &
  generalised spike-wave discharges
Application in Epilepsy
Types of EEG Epileptiform Activity

• Focal
  – Focal spikes (interictal)
  – Focal seizures (ictal)

• Generalised
  – Generalised spike-wave (GSW) (interictal)
  – GSW – Absence seizure (ictal)
The localisation problem in epilepsy

• Pre-operative assessment of drug-resistant cases
  – Aim: identify focus and suitability for resection
  – Methods:
    • EEG/MEG (visual, source analysis)
    • MRI
    • Video-telemetry
    • PET, SPECT

• Unclear? Conflicting?
  – Consider intracranial EEG
Focal spike

- Brief (<100ms)
- Unpredictable
- Sub-clinical
- Amplitude: ~10’s of μV
- Spatially linked to the focus
- Generator model: small cortical dipolar patch
- Paroxysmal Depolarisation Shifts (PDS): Excitatory and inhibitory signalling
  - Rapid bursts of action potentials riding on a slower wave of depolarisation
- ‘Pure EEG events’ / Mini seizures?
- Why does a spike occur (when it does)?
- Associated HRF?
General methodology

• Patient selection:
  – High EEG activity (spike rate)
  – Pre-implantation of intracranial electrodes

• Data acquisition strategy
  – Subject at rest
  – Simultaneous, continuous EEG-MRI
    • fMRI:
      – GE EPI BOLD [/ +ASL]
      – Whole-brain coverage (no prior hypothesis) [ASL: limited coverage]
    • EEG:
      – 12-64 channels
      – On-line artefacts removal

• GLM (SPM)
  – EEG -> fMRI
  – Motion effects
  – Thresh.: FWE <0.05 (corr.; GRF and uncorrected);
  – No min. cluster size
FMRI model building in Epilepsy (I)

1. **EEG events of interest**
   - Detection
   - Categorisation / grouping

2. **Event representation**
   - Individual brief events (spikes)
   - Runs of / long events

3. **Effects of no interest**
   - Motion
1. EEG events in fMRI time
   ➢ Vector of onsets for each event type

2. BOLD response for each event models

3. Linear model of BOLD
   ➢ convolution of 1 and 2
Focal epilepsy
Focal epilepsy: Seizure

Case summary:
- Tonic-clonic seizures
- MRI: normal
- Left temp. spikes
- EEG-fMRI: electrographic seizure

[Salek-Haddadi et al. 2002]
The HRF in Focal Epilepsy

Fitted Fourier basis set:

25 μV
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
ECG1-ECG2

fitted response +/- standard error

[Lesieux et al., 2001]
The HRF in Epilepsy: Non-canonical responses

Case 8: Left temporal spikes

Fourier basis set

HRF+TD model

Time-shifted Fourier model

HRF+TD
Scalp EEG sensitivity / bias
The baseline / sensitivity problem

Inside the brain
On the scalp
No EEG activity... What to do?

Spatial ICA of fMRI time series
Problems:
  Multiplicity of components
  Meaning
(Solution:)
  IC fingerprinting [De Martino et al., 2007]

Epilepsy result:

[De Martino et al., 2007]

[Rodionov et al., 2007]
Generalised epilepsies
(generalised spike wave [3Hz])
Generalised discharge: Spike & wave

Widely distributed over the cortex

Underlying neurophysiology:

- Thalamo-cortical circuitry; neocortical origin \([\text{Timofeev & Steriade, 2004}]\)

- **Spike**: rhythmic PDS's (similar to focal spikes)

- **Wave**: hyperpolarisation: cortical/thalamocortical ‘silence’

Interictal vs. ictal (‘absence seizure’)

- Effect of duration of discharge epoch / observation

Haemodynamic correlates?
EEG-fMRI of absence seizures

Case report:
Juvenile Absence Epilepsy
MRI normal

Regressor:

SPM:

[Salek-Haddadi et al., 2003]
EEG-fMRI of absence seizures - QS 1.5T series

Group analysis

N=18

SGE

Thalamus↑

↑

↓

↓

↑

↑

↑

(a)

N=10

(random effects)

[Hamandi et al., 2006]
Precuneus / Vigilance / Epilepsy
Altered vigilance:
- Focal spikes
- Absence seizures

Sleep

Vegetative state

General anaesthesia

“Default mode”

Rest

Perception + action

[Gusnard DA, Raichle ME]
Theories of GSW generation

- The historical debate: thalamus versus cortex in pathophysiology of GSWDs → from the “Centroencephalic Theory” to the “Corticoreticular Theory”

- Most of the evidence comes from invasive electrophysiological and neurochemical recordings in animals. Few observations in humans (PET, SPECT, H-MRS) (Bernasconi 2003; Prevett, 1995; Yeni, 2000)
Dynamic causal models of GSW generation

• Thalamus
• Frontal cortex (medial or middle frontal gyrus, BA10)
• Precuneus (BA7)
Dynamic causal models of GSW generation

Model A: (Centrencephalic)
- GSW drives BA7 and BA10
- BA10 drives thalamus

Model B: (Cortico/corticoreticular)
- GSW drives BA7 and BA10
- BA10 drives thalamus

Model C: (Precuneus theory)
- GSW drives BA7 and BA10
- BA10 drives thalamus

[Vaudano, submitted]
Dynamic causal models of GSW generation

**Results**

Model A (Thalamus) in 2/9

Model B (Frontal) in 0

Model C (Precuneus) in 6/9

(chance probability <0.008)
“Neuroelectric” / “neuronal currents” / “direct detection” MRI
Neuro-electric MRI of GSW?

[Liston et al., 2005]
Concluding remarks

• EEG-fMRI
  – Ensures coherent datasets
  – Allows study of spontaneous variations in brain activity
  – Has pros and cons of both modalities

• Implementation remains demanding
  – Data quality: artefact correction and quality control

• What does EEG-fMRI image?
  – EEG generators (~) + downstream effects
  – Networks: some new insights into causality

• Future:
  – Balance of benefits vs. costs?
  – Symmetric fusion: EEG & fMRI generative model
Team & collaborators

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