BASICS OF FMRI FOR COGNITIVE NEUROSCIENTISTS

John P O’Doherty

CALTECH
1. A brief history of functional localization
2. A brief overview of brain imaging techniques
3. An introduction to fMRI experimental design
4. An introduction to fMRI analysis
A brief history of functional localization in the brain
Phrenology
Franz Joseph Gall (1758-1828)

(1) Mind can be dissociated into separate components
(2) These components are located in anatomically distinct areas
(3) These components can be measured by the protuberance of the skull!

Psychograph circa 1934
Henry C. Lavery

• 1954 parts
• continuous motor driven belt containing statements about 32 mental faculties
• measured via 32 probes each with 5 contact points in the headpiece.

• Now in the ‘Museum of questionable medical devices’. Minnesota
Gall’s phrenological ‘organs’

Impulse to propagation
Tenderness for the offspring, or parental love
Friendly attachment or fidelity
Arithmetic, counting, time
Murder, carnivorousness
Mechanical skill
Comparative perspicuity, sagacity
Larceny, sense of property
Metaphysical perspicuity
Pride, arrogance, love of authority
Wit, causality, sense of inference
Ambition and vanity
Poetic talent
Circumspection
Good-nature, compassion, moral sense
Aptness to receive an education
Mimic
Sense of locality
Theosophy, sense of God and religion
Recollection of persons
Perseverance, firmness
Faculty for words, verbal memory
Pierre Flourens (1794-1857)

Pioneered experimental brain lesions in rabbits and pigeons

- Scientific tests of the claims of the phrenologists

- Showed that lesions of cerebral cortex abolished perception, motor ability, judgment

- Lesions of Cerebellum affected motor co-ordination/ balance

- Lesions of medulla oblongata caused death → role in vital functions

Couldn’t separate out different types of memory and cognition - concluded that memory and cognition relatively diffuse around the brain.
Broca’s aphasia – language production deficit located to left anterior part of the brain (inferior frontal gyrus)

Often credited as first report of cerebral localization

Similar report submitted earlier by Marc Dax (1771-1837)
Korbinian Brodmann (1868-1918)

52 distinct divisions of the cortex based on cytoarchitectonic differences
Karl S. Lashley (1890-1958)

Challenged the dominant ethos of cortical localization

1. The *Equipotentiality* Principle: all cortical areas can substitute for each other as far as learning is concerned.

2. The *Mass Action* Principle: the reduction in learning is proportional to the amount of tissue destroyed, and the more complex the learning task, the more disruptive lesions are.
Modern structural and functional brain imaging
a very brief overview
Modern brain imaging

- **Structural Imaging Techniques**
  - Computed Tomography
  - Magnetic Resonance Imaging

- **Functional Imaging Techniques**
  - Positron Emission Tomography
  - Functional Magnetic Resonance Imaging
Aims of Structural Imaging

- Clinical uses – diagnostic tool for stroke, haemorrhages & tumors.
- Lesions studies: associating damage to particular structures with deficits.
  - Probing structure/function relationship using patients
- Localizing increased neuronal activation identified with functional imaging techniques
Magnetic Resonance Imaging (MRI)

- Images are derived from signals transmitted by hydrogen nuclei in the brain.
- 70% of body = water = $\text{H}_2\text{O}$
- The hydrogen nucleus (H) consists of a single proton.
- The proton can be pictured as a charged sphere rotating on its axis.
MRI – Effect of Magnetic Field

- All of the protons are randomly aligned.
- Therefore the sample has no net magnetisation.

(Earth's magnetic field has a very small effect)
MRI – Effect of Magnetic Field

- Protons will align WITH or AGAINST the magnetic field.
- Due to energy considerations there is a VERY SMALL excess aligned with the field
  ⇒ small net magnetisation aligned with the field.
MRI – Radiofrequency Pulses

- If energy is provided in the form of a radiofrequency pulse, more of the protons can align against the external field.
- Reverses direction of net magnetisation.
MRI – Radiofrequency Signal

- However, after a short time, the energy is released and the protons realign to their previous state.
MRI – Types of Contrast

- Rate at which this realignment occurs differs for different tissue types.
- Possible to change timings involved in collecting the images & ‘weight’ the signal intensities in image for different tissue types.

T1: wait short time before sampling
- most useful for anatomical detail

T2: wait longer time before sampling
- most useful for pathological changes.
MRI – Clinical uses

T1: most useful for anatomical detail

T2: most useful for pathological changes.

CSF
grey matter
white matter

CSF/oedema

white matter
grey matter
Magnetic Resonance Imaging (MRI)

- **Advantages:**
  - Flexible – different kinds of images can be collected
  - Superior spatial resolution
  - No radiation exposure

- **Disadvantages:**
  - Expensive (compared to CT)
  - Unsuitable for claustrophobics
  - Strong magnet field
  - Not suitable for patients with implanted metal or pacemakers.
Aims of Functional Imaging

• Infer involvement of brain areas in particular tasks/cognitive functions using non-invasive techniques.
Angelo Mosso
1846 -1910

The brain itself is an excessively vascular organ, a sponge full of blood, in fact; and another of Mosso’s inventions showed that when less blood went to the arms, more went to the head. The subject to be observed lay on a delicately balanced table which could tip downward either at the head or at the foot if the weight of either end were increased. The moment emotional or intellectual activity began in the subject, down went the balance at the head-end, in consequence of the redistribution of blood in his system. But the best proof of the immediate afflux of blood to the brain during mental activity is due to Mosso’s observations on three persons whose brain had been laid bare by lesion of the skull. By means of apparatus described in his book,[29] this physiologist was enabled to let the brain-pulse record itself directly by a tracing. The intra-cranial blood-pressure rose immediately whenever the subject was spoken to, or when he began to think actively, as in solving a problem in mental arithmetic. Mosso gives in his work a large number of reproductions of tracings which show the instantaneity of the change of blood-supply, whenever the mental activity was quickened by any cause whatever, intellectual [p.99] or emotional. He relates of his female subject that one day whilst tracing her brain-pulse he observed a sudden rise with no apparent outer or inner cause. She however confessed to him afterwards that at that moment she had caught sight of a skull on top of a piece of furniture in the room, and that this had given her a slight emotion.

The fluctuations of the blood-supply to the brain were independent of respiratory changes,[30] and followed the quickening of mental activity almost immediately. We must suppose a very delicate adjustment whereby the circulation follows the needs of the cerebral activity. Blood very likely may rush to each region of the cortex according as it is most active, but of this we know nothing. I need hardly say that the activity of the nervous matter is the primary phenomenon, and the afflux of blood its secondary consequence.

From William James. The Principles of Psychology (1890)
Baseline Brain Activity

• Brain at ‘rest’ accounts for:
  – 20 % of total oxygen consumption
  – 25 % of total glucose consumption

• Energy consuming processes at ‘rest’:
  – Maintenance of the ‘resting’ potential (Na⁺/K⁺ ATP pump)
  – Tonic firing of neurons ⇒ background level of synaptic activity
  – General cell maintenance of neurons and glia.
Three markers of increased brain activity:
- Increased blood flow
- Increased consumption of glucose
- Increased consumption of oxygen
Outline:

• **Structural Imaging Techniques**
  – Computerised Tomography
  – Magnetic Resonance Imaging

• **Functional Imaging Techniques**
  – Positron Emission Tomography
  – Functional Magnetic Resonance Imaging
Positron Emission Tomography (PET)

- Radioactive labelled molecules injected or inhaled
- Assess distribution of labelled molecule in brain.

- Positron emitted from an unstable nucleus
- Collides with an electron
- Releases two photons with equal and opposite velocities
Positron Emission Tomography (PET)
Positron Emission Tomography (PET)

- Possible to incorporate positron-emitting nuclei into many molecules of biological interest.
- For functional studies:
  - $^{18}$F-fluoro-deoxyglucose ⇒ glucose metabolism
  - $^{15}$O$_2$ ⇒ oxygen consumption
  - $\text{H}_2^{15}$O ⇒ local blood flow
Positron Emission Tomography (PET)

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- For functional studies:
  - $^{18}\text{F}$-fluoro-deoxyglucose $\Leftrightarrow$ glucose metabolism
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  - $\text{H}_2^{15}\text{O} \Leftrightarrow$ local blood flow
Positron Emission Tomography (PET)

- $\text{H}_2^{15}\text{O}$ has a half-life of 2.07 minutes
- One scan = 1 minute duration
- 10-15 minutes interval between successive scans
- Up to 12 scans allowed
- Each scan corresponds to a particular experimental condition
- A structural MRI scan is often collected too
  - Useful for localizing any differences in activation.
Positron Emission Tomography (PET)

‘REST’ blood flow maps:
Baseline level of blood flow measured

‘ACTIVE’ blood flow maps:
Blood flow during hand movement measured

‘Significant difference’ maps:
Significant differences in blood flow between the maps for each ‘condition’.
Positron Emission Tomography (PET)

**Advantages:**
- Quantitative: able to measure amount of blood flow or glucose/oxygen consumption
- Large changes in signal – easy to detect

**Disadvantages:**
- Image resolution fairly poor (10-20 mm)
- No temporal information
- Each scan fairly long – not suitable for some experimental conditions
- Invasive – injection of tracer required
- Exposure to radiation.
Functional MRI

- Uses MRI scans to access information about changes in oxygenation levels in the brain.

- Rate at which radiofrequency energy is lost can be influenced by alterations in the local oxygenation levels of the blood in an area of increased neuronal activity.
Functional MRI: *haemoglobin*

- This is due to magnetic properties of blood related to its oxygenation.
- Haemoglobin: primary carrier of oxygen
- Contains four Fe$^{2+}$ ions.
- Deoxyhaemoglobin is *paramagnetic* - *Slightly increases local magnetic field*
- Oxyhaemoglobin does not have this property.
- Magnetic field around deoxyhaemoglobin causes nearby protons to lose their radiofrequency energy more rapidly
  - ⇒ lower MR signal
  - ⇒ image appears darker.
Functional MRI

- Increased proportion of deoxyhaemoglobin.
- MRI signal lower = darker
Functional MRI

- Increased proportion of deoxyhaemoglobin.
- MRI signal lower = darker

- Decreased proportion of deoxyhaemoglobin.
- MRI signal higher = brighter
Functional MRI: \textit{BOLD contrast}

- This change in signal intensity due to the relative proportions of oxy- and deoxy-haemoglobin is called:

\textbf{Blood Oxygenation Level Dependent contrast}

= \textit{BOLD Contrast.}
Underpinnings of BOLD signal

From Logothetis and Wandell, Annual Review of Physiology, 2004
Correlates of Brain Activity

- Three markers of increased brain activity:
  - Increased blood flow
  - Increased consumption of glucose
  - Increased consumption of oxygen
Functional MRI
Functional MRI
Functional MRI
Functional MRI

• An increase in MRI signal intensity occurs.
• Increase in oxygenated blood supply to the area massively overcompensates for the increased consumption of oxygen.
Functional MRI: *BOLD* response
Functional MRI: \textit{BOLD response}
Functional MRI: BOLD response
Functional MRI: BOLD response
Functional MRI: *BOLD response*

% signal change

Seconds
Functional MRI: *BOLD response*
Functional MRI: *temporal resolution*

- Possible to test the effect of multiple conditions within one continuous time series.

![Diagram showing hand movements and MRI signal](attachment:diagram.png)
Functional MRI: *temporal resolution*

- Possible to test multi-stage complex tasks such as motor preparation and motor execution
Functional MRI

- **Advantages:**
  - Allows more ‘real world’ presentation of tasks
  - Superior temporal resolution than PET
  - Superior spatial resolution than PET
  - No tracer required & no radiation exposure
  - Uses standard modern MRI technology

- **Disadvantages:**
  - Noisy – not ‘real world’ environment
  - Unsuitable for claustrophobics
  - Not suitable for patients with implanted metal or pacemakers.
## Summary of Functional Imaging

<table>
<thead>
<tr>
<th></th>
<th>PET</th>
<th>fMRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expensive</td>
<td>Expensive</td>
<td>Relatively cheap</td>
</tr>
<tr>
<td>Poorer spatial resolution</td>
<td>Poorer spatial resolution</td>
<td>Better spatial resolution</td>
</tr>
<tr>
<td>Poorer temporal resolution</td>
<td>Poorer temporal resolution</td>
<td>Better temporal resolution</td>
</tr>
<tr>
<td>Silent</td>
<td>Silent</td>
<td>Noisy</td>
</tr>
<tr>
<td>Radiation exposure</td>
<td>Radiation exposure</td>
<td>No radiation exposure</td>
</tr>
<tr>
<td>Can measure receptor binding</td>
<td>Can measure receptor binding</td>
<td>Cannot image receptor binding</td>
</tr>
<tr>
<td>No problems with signal dropout</td>
<td>No problems with signal dropout</td>
<td>Signal loss due to field inhomogeneities</td>
</tr>
</tbody>
</table>
Electroencephalography (EEG) & Magnetoencephalography (MEG).
Electroencephalography (EEG) & Magnetoencephalography (MEG).

• Both methodologies detect the electromagnetic effects of the activity of populations of neurons - if activated in unison the combined electrical currents summate to form a single current dipole.

• The strength of the dipole is defined by the summation of post-synaptic potentials occurring in the dendrites of a large number of neurons, as these potentials have a relatively long time course compared with the short pre-synaptic action potential spikes of the nerve axon, and are hence more likely to summate.

• Both EEG and MEG measure secondary manifestations of these primary events: changes in electromagnetic signals on the scalp.

• EEG measures electrical fields on the scalp

whereas,

• MEG measures magnetic fields generated by electrical activity at scalp
• The signals acquired in both EEG and MEG studies require amplification before processing can occur. This is particularly important in MEG studies, as the magnetic field generated by the source activity is very small, requiring both superconductive magnetometers and amplifiers, named Superconductive Quantum Interference Devices (SQUIDS).

• The scalp signals obtained using MEG are undistorted as the magnetic permeability of the brain is close to that of a vacuum.

• Signals measured in EEG studies are subject to distortions due to the inhomogeneities in tissue conductivity through the brain. ➔ Less accurate and reliable inverse solutions for EEG than MEG.

• Information from high spatial resolution imaging modalities, such as positron-emission tomography (PET) and functional MRI (fMRI), can also be combined with electromagnetic data to constrain the possible solutions of the inverse problem.
• For both techniques, localization of the source of the scalp measurements requires the solution of the *inverse problem*; there is no unique solution to the problem of determining the combination of primary sources that induce the electromagnetic signals observed at the scalp.

➤ **Major drawback of EEG/MEG** is the loss of spatial information (e.g. deep or radial sources with MEG) or uncertainty as to the location of the neural generators (due to the inverse problem).

➤ **Major advantage of EEG/MEG** is the fine temporal resolution (in the order of msecs)
**EEG – oscillations in brain activity**

- *Awake* — Low Voltage — Random, Fast
- *Drowsy* — 8 to 12 cps — Alpha Waves
- REM Sleep (D Sleep) — Low voltage — Random, Fast Sawtooth Waves
- Stage 1 — 3 to 7 cps — Theta Waves
- Stage 2 — 12 to 14 cps — Sleep Spindles and K Complexes
- Delta Sleep (S Sleep) — ½ to 2 cps — Delta Waves

**Event-related Potential (ERP)**

- Stimulus Onset
- Peak Latency
- Peak to Peak
- Base to Peak

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Event-related Potential (ERP)

- Stimulus Onset
- Peak Latency
- Peak to Peak
- Base to Peak
Imaging in the grand scheme of things

Log Size (mm)

Log Time (seconds)

Non-Invasive

Invasive
Why bother do human brain imaging?

Possible Critiques

• Modern ‘phrenology’ or ‘blobology’ – doesn’t tell you anything.

• Assumption of spatially distinct modular regions is wrong

• You can tell everything you need to know about cognitive architecture from looking at behavior, measuring reaction times etc.

• Link between neural activity and fMRI signal not well understood

• Purely correlative technique – activity could be an epi-phenomenon -How do we know because something is ‘active’ that this region is critical for a given function/behavior?

• Spatial/temporal resolution not good enough to see anything meaningful

• Assumption that computations in a region are always associated with an increase in overall levels of neural activity in that region may not always be valid.

• Findings not reproducible!
An introduction to experimental design in fMRI
Steps in experimental design

1/ Establish a hypothesis

2/ Determine how to test hypothesis

3/ Choose appropriate fMRI paradigm
Steps in experimental design

1/ Establish a hypothesis

Q. What kind of hypothesis is appropriate for an fMRI study?

Some flavors of hypothesis:

- Neuroanatomically (spatially) specific: area X will be engaged in condition Y while performing task Z.

- Temporally specific: activity in area X will be engaged at time-point T1 during condition Y, but at time T2 during condition Z.

- Hypothesizing a specific relationship between neural activity and some external variable e.g. activity in area X is proportional to F(Y) where Y = external variable (e.g. pleasantness, computational learning signal), and F is some linear or non-linear transformation of Y.
Different levels of inference in fMRI during hypothesis testing:

Spatial Working Memory

Different levels of inference in fMRI during hypothesis testing:

• Hemodynamic

From Funahashi et al., (1989)


• Neuronal

From Funahashi et al.; (1989)

• Psychological

Neural activity in DLPFC is involved in maintaining spatial information on-line during delay period

• Computational

From Zipser et al., 1993
STEPS IN EXPERIMENTAL DESIGN

2/ DETERMINE HOW TO TEST YOUR HYPOTHESIS

THE PRINCIPLE OF COGNITIVE SUBTRACTION
LIMITATIONS OF COGNITIVE SUBTRACTION

• Assumes all cognitive factors are linearly additive
  BUT, what if they interact?

Factorial design

Motor

Visual

off              on

off              on
Question: How can we design an fMRI experiment to localize the ‘TEAPOT’ processing area?

- Teapots
- Other objects
- Scrambled teapots
- Fixation (rest)
CHOOSE YOUR CONTROL CONDITION CAREFULLY

Teapot area = Nature paper!
DEALING WITH CONFOUNDS

• EXAMPLE: Want to compare neural activity when choosing to get reward vs choosing to avoid punishments.

• However, average reaction times DIFFER between these two conditions.

• Therefore – difference in activity between conditions could reflect RT differences and not some interesting difference in the underlying decision processes

• Q: How to deal with this?

• Refine your experimental design to keep these RT differences to a minimum

• Sub-select trials from each decision type that are MATCHED for reaction times

• Include reaction times as an effect of no interest in the analysis and regress these effects out of the data.
3/ CHOOSE FMRI PARADIGM

A basic taxonomy of fMRI designs

• BLOCK

• EVENT-RELATED

• MIXED
BLOCK DESIGNS
- apply stimulus or perform task repeatedly over a long interval of time (typically 15-30 secs)

Alternating: ABABABABABABABABAB
Alternating with rest: ARBRARBRARBRARBRARBR
Cyclical – 3 conditions: ABCABCABCABCABCABC
Randomized order: CABABCBCABACCCBA

(order effect)
What does signal look like?

One session

Passive word listening versus rest

7 cycles of rest and listening

Each epoch 6 scans with 7 sec TR

Question: Is there a change in the BOLD response between listening and rest?

Time series of BOLD responses in one voxel

Stimulus function
Why use BLOCK designs?

ADVANTAGES

• Maximally efficient for signal detection (induces high experimental variability)

• Easy to implement

• Easy to analyze

• Useful for picking up state-related changes or slow varying cognitive processes – e.g. ‘attention’, ‘affective state’, ‘arousal’.
Why use BLOCK designs?

DISADVANTAGES

• Signals are susceptible to stimulus correlated movement artifact or other causes of signal artifacts with regular periodicity. Long block lengths can get confounded with low frequency scanner drift (or signals can get cut off by high pass filter).

• Cannot separate out individual responses to specific trials.

• Poor temporal resolution.

• Poor estimability of underlying response profile.

• Some cognitive/neural processes may habituate early – hence wouldn’t be detected with block design.

• Could confound different psychological variables of interest – e.g. anticipation vs receipt of reward.
• **EVENT-RELATED DESIGNS**

Measure responses to single events e.g single presentation of a stimulus (for e.g. 500msecs), or a single trial of a particular task. Average over large numbers of those single events to obtain statistical power.
VARIETIES OF EVENT-RELATED DESIGN

- **SLOW EVENT-RELATED DESIGN**
  
  Can be fixed length or variable length – ‘jittered’

Inter-stimulus-interval or Inter-trial-interval
**RAPID EVENT-RELATED DESIGN**

- Based on notion of linear deconvolution
- Usually (but not necessarily) assumes LINEARITY during summation of BOLD signal response.

Again could jitter this

3 secs

‘Null’ event

same event can be repeated on next trial
MIXED DESIGN

Events: Teapots (T), Other (O), Null (N)
Blocks: Attend or Don’t Attend
Why use event-related designs?

ADVANTAGES

• Good estimability of single trial responses:
  - helps with inference about underlying neuronal activity –
    e.g. latencies, sustained vs phasic, bimodal etc.

• Much greater *psychological* validity (usually)

• Enables post-hoc sorting of trials (e.g. remembered
  vs. forgotten items; predicted vs unpredicted, correct
  vs incorrect etc.)

• Can separate out multiple cognitive processes within
  a trial e.g. anticipation vs receipt of reward

• Naturally lends itself to trial by trial correlational analyses
  with some external variable – e.g. parametric signal
  of preference; time-series derived from a computational model:
  model-based fMRI.
Why use event-related designs?

DISADVANTAGES

• Weaker detection power than block designs (in general)
  Note: Detectability varies considerably as a function of the actual design used – the more likely it is that an event of the same type will occur sequentially (with appropriate additional contraints) the greater the detectability.

• Slow event-related designs – are particularly inefficient (detectability wise), but best for estimated shape of underlying response.

• Rapid event-related designs can give better detectability – can also get good estimation, BUT, usually assumes linearity of BOLD response
  - Can model non-linearity effects (interactions between trials in time)
  - Linearity assumption is usually not violated for ISIs of > 2 to 3 secs.

• Rapid event-related designs often involve use of highly contrained basis function sets such as a ‘canonical’ HRF ➔ this involves making a strong assumption about the SHAPE and TIMING of the underlying hemodynamic response.

BUT – we know this can vary by region and task.
So then, WHICH to use?

DEPENDS…..

• Psychological/task constraints
  - many designs now require event-related protocols, but not necessarily ALL.

• Experimental sensitivity needed – actual effect size of phenomenon being studied.

……...of course often don’t know this in advance!

• Can often take a two-pronged strategy:
  
  - BLOCK design to LOCALIZE regions showing sensitivity to a given effect

  THEN

  - Event-related design to investigate response profile in this area in more detail.