FSL Course

Introduction to Imaging

- Basic Anatomy
- Applications of MRI in Neuroimaging
- Introduction to MRI Acquisition & Analysis
  - Structural MRI
  - Diffusion MRI
  - Functional MRI
- Complementary Techniques and Methods
- Brain Extraction
The brain is full of neurons. These are organised into two types of “tissues”:
- Grey Matter
- White Matter
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- Grey Matter
- White Matter
Neurons are densely connected and have many dendrites.
Neurons are densely connected and have many dendrites. Axons conduct electrical signals and are surrounded by myelin. Myelin is a major factor in determining the MR signal and contrast.
Applications of MRI in neuroimaging
Neuroimaging research examples: neuroscience

- Structural MRI
- Diffusion MRI
- Functional MRI (task)
- Functional MRI (resting)
Neuroimaging research examples: neuroscience

- Study of taxi drivers showing structural plasticity

Maguire et al., PNAS, 2000

Discussion

The data presented in this report provide evidence of regionally specific structural differences between the hippocampi of licensed London taxi drivers compared with those of control subjects. Taxi drivers had a significantly greater volume in the posterior hippocampus, whereas control subjects showed greater volume in the anterior hippocampus. The converging results...
Neuroimaging research examples: Asperger Syndrome

- White matter integrity - imaging tissue nature change
- Differences in brain connectivity in multiple tracts

Green = white matter tract; Red/Yellow = statistically significant change in FA

Roine et al., Molecular Autism, 2015
Neuroimaging research examples: stroke therapy

Single subject: responder

Unaff. hand (right)

Pre 1

Pre 2

Aff. hand (left)

Post 1

Post 2

Group: Correlations with improvement

Functional MRI (task)

Johansen-Berg, et al., Brain 2002
Distinct patterns of brain activity in young carriers of the APOE-ε4 allele

Nicola Filippinib, Bradley J. Maclintoshb, Morgan G. Houghb, Guy M. Goodwina, Giovanni B. Frisonic, Stephen M. Smithb, Paul M. Matthewsde, Christian F. Beckmannb,e, and Clare E. Mackaya,b,1

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The APOE ε4 allele is a risk factor for late-life pathological changes that is also associated with anatomical and functional brain changes in middle-aged and elderly healthy subjects. We investigated structural and functional effects of the APOE polymorphism in 18 young healthy APOE ε4-carriers and 18 matched noncarriers (age range: 20–35 years). Brain activity was studied both at rest and during an encoding memory paradigm using blood oxygen level-dependent fMRI. Resting fMRI revealed increased “default mode network” (involving retrosplenial, medial temporal, and medial-prefrontal cortical areas) coactivation in ε4-carriers relative to noncarriers. The encoding task produced greater hippocampal activation in ε4-carriers relative to noncarriers. Neither result could be explained by differences in memory performance, brain morphology, or resting cerebral blood flow. The APOE ε4 allele modulates brain function decades before any clinical or neurophysiological expression of neurodegenerative processes.

Functional MRI (resting)
Neuroimaging research examples: Surgical planning

Diffusion MRI + Functional MRI (task)

(Bartsch et al., JMRI 2006)
Neuroimaging research examples: Parkinson’s Disease

Structural MRI + Diffusion MRI

Look at tracts connected to regions of structural change

Menke et al., Brain 2013
FSL Course

Introduction to MRI acquisition and analysis
MRI Analysis

• MRI is:
  • noisy
  • variable/configurable

• Analysis is:
  • based on statistics
  • has many options/alternatives
  • has more than one “right” way (but many wrong)

• This course aims to:
  • explain aspects needed to make good choices in the analysis, acquire good images, interpret the results
  • present information relevant to using the methods, but not cover all the details of the inner workings
Overview

- Variety of acquisitions
- Measurement basics
- Limitations & artefacts
- Analysis principles
- Acquisition tips

- Structural MRI
- Diffusion MRI
- Functional MRI
- Complementary techniques
Structural MRI

- Images gross brain anatomy
- Time depends on SNR & resolution (typ. 3-15 mins)
- Many different (and good) varieties of sequences to acquire these images

$T_1$-weighted  $T_2$-weighted  Proton Density
Analysis of Structural MRI

- Quantify tissue volumes and structure shape/size

Tissue types: GM / WM / CSF

Sub-cortical structure & shape

Cortical surfaces & thickness

Local GM changes
Structural MRI Measurement

• 3 main quantities involved here:
  • Density of water & fat (proton density)
  • $T_1$ relaxation time
  • $T_2$ relaxation time
Structural MRI Measurement

• 3 main quantities involved here:
  • Density of water & fat (proton density)
  • $T_1$ relaxation time
  • $T_2$ relaxation time

• Relaxation times depend on many things (e.g. molecular tumbling speed) but are sensitive to micro-environment and hence “tissue type”

• Intensity is usually a complicated weighting of different factors
Structural MRI “Limitations”

- Does *not* measure tissue type (GM/WM/CSF) directly
- It is not quantitative
- $T_1$ and $T_2$ values vary within GM and WM
  (but this can be interesting!)
- Does not distinguish bone from air
- Contrast can be poor/variable in subcortical regions
- Single sequence does not show all pathologies
- Artefacts and noise
There is always a trade-off in MRI between acquisition time, resolution and noise (Signal to Noise Ratio = SNR).

For analysis it is Contrast to Noise Ratio (CNR) that is often more important, and contrast depends on MR sequence too.
RF Bias (B₁ inhomogeneity)

- Non-uniform RF field causes smooth variations in intensity
- Can sometimes be very large
  - less smooth for higher field (e.g. 7T) & multi-coil arrays
- Need to compensate in analysis
Structural MRI Artefacts

**Physiological**

Motion can be problematic - minimise at acquisition

**Hardware/settings**

Ghosting normally very minor

Wrap-around should always be avoided
Structural MRI Artefacts

Hardware-related

RF Interference

RF Spiking

+ others... e.g. chemical shift (fat-water misaligned)

Most are serious but uncommon (easy to identify)
Artefact-Detection Device

LOOK AT YOUR DATA!
Structural MRI: Analysis

Basic stages in the structural analysis pipeline:

- Brain Extraction
- Segmentation (structure)
- Segmentation (tissue-type)
- Registration (alignment)
Structural MRI: Analysis

Later stages in the structural analysis pipeline:

Statistics!
(often non-parametric)

Needed to investigate group-level changes/relations

Local GM changes

Local shape changes

Local thickness changes
Basic tips for acquisition

• T₁-weighted images tend to be the best for the SNR/time/resolution tradeoff (1mm voxels are typical)

• Use the locally optimised sequence on your scanner
  - there are many sequences names/types that give T₁-weighted images and most are equally good

• If subjects are likely to move a lot then (offline) averaging several shorter acquisitions can be better

• Sub-cortical contrast can be enhanced with different sequences or parameter choices

• Turn on some fat-suppression (helps brain extraction)

• Isotropic voxels are much better for analysis in general

• Do not do upsampling on scanner (sometimes the default)
Structural MRI (2)

- By changing timing and signals (RF/gradsents) of MR sequence can null certain “tissues” or flows
- Useful for highlighting lesions/pathologies
- Also can give better sub-cortical contrast
  - e.g. Brainstem; Globus Pallidus internal/external
Structural MRI (3)

- By sensitising the sequence to different properties can detect other features of tissue:
  - SWI/QSI: S=susceptibility; magnetic field changes due to iron content (primarily) and myelin/WM
  - MT: Magnetisation Transfer; bound/free water
  - Veno/Angio-grams: flow/blood iron/contrast agent
**Structural MRI**

Many other types of structural MRI, for example...

- Susceptibility-Weighted Imaging (SWI)
  - Quantitative Susceptibility Imaging (QSI)
- Magnetization Transfer (MT)
- MR Spectroscopy (MRS)
- Angiograms & Venograms
- Quantitative $T_1$ and $T_2$ maps (relaxometry)
- Myelin maps
- $B_0$ map (fieldmap)
- $B_1$ map (RF)

**Sensitive to:**
- iron
- (and myelin)
- chemical species/
  environment
- arteries & veins
- tissue $\mu$structure
- myelin
- fields
- within head
Diffusion MRI

• Measures microstructure directionality and “integrity”, particularly in WM
• Provides information on anatomical connectivity
• Need to acquire many “directions”: 5-30 min scan
Analysis of Diffusion MRI

Surrogate measures of *microstructure*
Local WM structure via tensor: directions, Mean Diffusivity (MD) and Fractional Anisotropy (FA) -
Analysis of Diffusion MRI

Probabilistic Tractography

Tractography traces connections via local directions
Probabilistic Tractography can be used for connectivity-driven segmentation.

Segmented seed region (thalamus) - based on highest target probability

Target masks
Diffusion MRI Measurement

• Based on movement (diffusion) of water
• Restricted more in some directions than others - gives most information about axon directions in WM

• Gives information about microstructure, but averaged over whole voxel

• Sensitive to one direction per image;
  ‣ lots of directions = lots of images

• Use FAST imaging (EPI) to get enough images
Mini MR Physics

Diffusion sensitizing (encoding) gradient

Gradient coils: create magnetic field changes in any direction

Moving spins in the gradient direction change “phase” and reduce in coherence (less signal)
Gradient coils: create magnetic field changes in any direction

Diffusion sensitizing (encoding) gradient

Moving spins in the gradient direction change “phase” and reduce in coherence (less signal)
Diffusion MRI “Limitations”

• Does not measure axon size/density directly
• Does not measure single fibres (only average groups)
  • More difficult to deal with crossing/kissing fibres
• Quantitative local measurements, but not connectivity
• More difficult to do in pulsatile regions (e.g. brainstem)
• More restricted by hardware and SNR
• Sensitive to fast imaging artefacts
Diffusion MRI Artefacts

Hardware-related

Eddy Currents

Distortion

+ Bulk/Pulsatile Motion ... plus all the structural artefacts

• Eddy currents: both acquisition and analysis fixes available
• Distortion due to $B_0$ inhomogeneity (air in sinuses)
  - acquisition-and-analysis related fixes needed
• Bulk motion is corrected for in acquisition (navigators)
• Pulsatile motion is more problematic
Diffusion MRI: Analysis

Basic stages in the diffusion analysis pipeline:

- Eddy Current & Motion Correction
- Probabilistic Tractography
- Fibre/Direction Modelling
- "Tensor" Fitting e.g. FA, MD

Summary of image-registration based methods for correcting EC-induced distortions:

- Haselgrove & Moore 1996
- Bodammer et al. 2004
- Bastin et al. 2001
- Rhode et al. 2004
- Andersson & Skare 2002

No additional scans needed for RHODE ITERATION.
Diffusion MRI: Analysis

Later stages in the diffusion analysis pipeline:

- **Statistics** (non-parametric)
- FA changes in WM tracts
- Tractography-based Segmentation

To investigate group-level changes/relations
Diffusion MRI: Acquisition

Basic tips for acquisition

• Best parameters can be quite hardware dependent (esp. gradients) so check what is optimised for your scanner
• In general, b-value of 1000-1500 s/mm\(^2\) and 60+ directions (tractography) or 12+ directions (FA, etc.) tend to give good results (but the more directions the better)
• Get one b=0 image for every 8-10 diffusion-weighted images
• Get even distribution of directions on a full sphere
• Choose a sequence that compensates for eddy currents (e.g. twice refocussed sequence, modified S-T, etc.)
• Get a fieldmap (B\(_0\)) for distortion correction - or alternatively, a blip-up-blip-down sequence (FSL tool - topup - out now!)
• Isotropic voxels (or close) are better for analysis generally
• Do not do upsampling on scanner (sometimes the default)
• Both single/multi-shell give good tractography
Functional MRI

- Measures haemodynamic response to neural activity
- Task-based or resting-state-connectivity
- Intrinsic contrast (BOLD) or explicit tag (ASL)
- Take many fast images (EPI): 5-60 min scan
Analysis of Functional MRI

Task FMRI

Tag

Control

Resting-State FMRI & Connectivity

ASL
Information Transfer:
- large changes in membrane potential leading to action potential
- chemical neurotransmission across synapses
Brain Physiology: Metabolic

Information Transfer:
- large changes in membrane potential leading to action potential
- chemical neurotransmission across synapses
Signalling Energy Use

Atwell and Laughlin, JCBFM, 2001
Magnetic Properties of Haemoglobin

Oxy-haemoglobin
Diamagnetic
(same as tissue)

Deoxy-haemoglobin
Paramagnetic
$\Delta \chi \approx 0.2$ ppm
Mini MR Physics: $T_2^*$ Effect

Metal artefact above (obvious)
BOLD effect (subtle version: reduction in signal)

<table>
<thead>
<tr>
<th>B₀ field within voxel</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change (uniform B₀)</td>
<td>Good Signal</td>
</tr>
<tr>
<td>Large change (inhomogeneity)</td>
<td>Loss of Signal</td>
</tr>
</tbody>
</table>
BOLD Effect

Magnetic field perturbed
- Dephasing of nearby spins
- Loss of signal

- arterioles
- capillary bed
- venules

- $\text{HbO}_2$
- $\text{Hbr}$
BOLD Effect

Increased Neuronal Activity

CBF

CBV

CMRO₂

Magnetic field less perturbed
Less dephasing
More signal

= HbO₂
= Hbr

arterioles
capillary bed
dip
overshoot
undershoot
stimulus
time

positive BOLD response

BOLD response, %

stimulus
A sequence of low resolution $T_2^*$-weighted volumes are taken during the FMRI experiment

- Optimised for BOLD sensitivity and speed
- Take one volume every 1-3 seconds
- Often take around 200 volumes (10 minutes)
- An FMRI volume is shown here in **orthogonal** view
Images - High Resolution MRI

- Need a single, high-resolution $T_1$-weighted image for each subject (not each session)
- Used to map activations onto
- Best way to identify anatomy
- Better accuracy for registration of results to standard space
Functional MRI “Limitations”

- Does *not* measure electrical activity
- Does *not* measure metabolic activity
- BOLD-FMRI is qualitative
- Sensitive to fast imaging artefacts
**Functional MRI Artefacts**

**Hardware-related**
- Distortion due to $B_0$ inhomogeneity (air in sinuses)
  - acquisition-and-analysis related fixes needed (fieldmap)
- Physiological noise is more problematic near the brainstem
  - acquire physiological measurements & do analysis fix
- Motion can also be a significant problem (some analysis fixes)

**Physiological**
- Signal Loss
- Physiological Noise

... plus most diffusion artefacts (not eddy currents) and all structural artefacts
Functional MRI “Limitations”

- Does not measure electrical activity
- Does not measure metabolic activity
- BOLD-FMRI is qualitative
- Sensitive to fast imaging artefacts
- Need good T$_2^*$ sensitivity
  - causes lost signal in inferior regions
- ASL suffers from worse SNR
Functional MRI: Acquisition

Basic tips for acquisition

• Use optimised sequences/protocol for your scanner/site
• Get fieldmap ($B_0$) for compensating distortion/signal-loss
  - blip-up-blip-down is not an option for functional MRI
• For inferior-frontal/temporal areas apply acquisition techniques to *minimise signal loss*
  - e.g. thin slices, slice angulation, z-shims, parallel imaging, ...
• Isotropic voxels (or close) are better for analysis generally
• Do not do upsampling on scanner (sometimes the default)
• For small FOV also take one single whole-brain EPI
• Biggest interaction of exp. design-acquisition-analysis so think carefully about all parts before acquiring data!
Complementary techniques

Invasive

Non-invasive

MEG / EEG

fMRI

PET

Lesions

Brain

Log size (m)

Log time (s)

Map

Column

Layer

Neuron

Dendrite

Synapse

Single unit

Patch clamp

Light Microscopy

Non-invasive

Invasive

Synapse

Layer

Column

Map

Brain

Log size (m)

Log time (s)
**Complementary techniques**

**Physiological Measures**

**electrical activity**
- excitatory
- inhibitory
- soma action potential

- EEG
- MEG

**metabolic response**
- ↑ glucose consumption
- ↑ oxygen consumption

**haemodynamic response**
- ↑ blood flow
- ↑ blood volume
- ↑ blood oxygenation

**FDG PET**
**autoradiography**

**H$_2^{15}$O PET**

**NIRS**

**optical imaging**

**fMRI**
Complementary techniques

Structural MRI:
- CT (bones/membranes/vessels/tumours)
- Histology (microstructure)

Diffusion MRI:
- Tracer studies (individual fibres)
- Histology (myelin/axon dimensions/glia)

Functional MRI:
- PET/SPECT (metabolic/ligands/low res.)
- EEG/MEG (electrical activity/high temporal res.)
- NIRS (haemodynamics/high temporal res.)
- TMS/TDCS (alter regional brain function)
- Electrodes (single cells/cell groups)
Complementary Methods: FreeSurfer

Cortical modelling and flattening Surface-based registration
Subcortical segmentation

- Model G-W surface, inflate sulci, then expand each cortical hemisphere to a spherical surface
- Align across subjects on the cortical surface
- Display activation on inflated/flattened surface
- Cortical thickness measurements
- Multi-subject FMRI stats on standard spherical surface (reduces subject variability)
- Subcortical segmentation
- Easy to pass data between FSL & FreeSurfer
BET: Brain Extraction Tool

Brain / non-brain segmentation

Preparation step for registration and segmentation

Eliminates non-brain tissues with highly variable contrast and geometry (e.g. scalp, marrow, etc.)
  - works best if some fat sat is used

Robust to bias fields (by using local intensity changes)

Works with a wide range of MRI sequences (T1, T2, etc.) and resolutions
Example Results

Brain Surface Model

Extracted Brain Surface
(not what we aim for here)
Example Results
Example Results

Want to remove the majority of non-brain structures, leaving all the brain intact. Leaving small pieces of non-brain is *unimportant for linear registration*, but it is important for segmentation.
And that’s all
And that’s all
... for now
Running FSL

• Main FSL GUI: type `fsl` and access the other GUIs through this
  • or type the name starting with a capital letter: e.g. `Melodic` (or `Melodic_gui` on Mac)

• Command-line (non-GUI) versions of programs are lowercase: e.g. `melodic`

• Command-line versions allow much more flexibility and the ability to *script* (automate)

• Viewing tool (FSLeyes) completely separate from processing and analysis

• Help via web-docs, usage messages, email list, ...
The quick guide for FSL is:

- DICOM - No
- NIFTI - Yes
- Analyze - sooo last century!

Just need to convert DICOM to NIFTI once, after acquisition, then run everything else with NIFTI.

Many tools available to do the conversion. For example:

- dcm2nii from mricron
- mri_convert from FreeSurfer
FSL Overview

Structural
- BET: brain extraction
- FAST: tissue segmentation
- FIRST: subcortical segmentation
- FLIRT: linear registration
- FNIRT: nonlinear registration
- FUGUE: EPI unwarping
- SIENA: atrophy analysis
- FSL-VBM: grey matter density

Functional
- FEAT: model-based FMRI analysis
- MELODIC: model-free FMRI analysis
- FLOBS: optimal HRF basis functions
- FABBER: perfusion analysis

Diffusion
- FDT: diffusion & tractography
- TBSS: voxelwise DTI analysis

Other tools
- FSLeyes: display tool
- Inference (randomise, SMM)
- Brain atlases
- POSSUM: FMRI simulator
- FSLUTILS misc. utilities e.g. fslmaths, fslstats, etc.
FSLeyes

- No built-in processing/analysis
- FMRI timeseries viewing (model vs. data)
- Interaction with several probabilistic atlases
- Load images with different resolution/FOV
FSLUTILS
misc command-line programs

• fslhd / fslinfo / fslval - show header info
• fslcreatehd - create header

• fslmerge - concatenate images in x/y/z/t
• fslroi - extract region-of-interest from 3D/4D
• fslsplit - split 4D image into lots of 3D volumes

• fslmaths - general image calculator
• fslstats - estimate summary image statistics
• fslmeants - extract mean/masked timeseries
• fslreorient2std - reorient image axes
FSLUTILS

misc command-line programs

• Each command-line tool provides a usage message when run with no *arguments* (i.e. options/inputs). For example:

```
$ fslsplit
Usage: fslsplit <input>
  fslsplit <input> [output_basename] [-t/x/y/z]
  -t : separate images in time (default behaviour)
  -x : separate images in the x direction
  -y : separate images in the y direction
  -z : separate images in the z direction
```

• Compulsory arguments look like `<this>`
• Optional arguments look like `[this]`
- A set of options looks like `[this/that/other]` where only one should be used in any command
• Any “double minus” args need an *equals sign* (with no spaces)
  e.g. `fsl_tsplot -i inputfile -o outputfile --start=2`
PRACTICAL

• Open laptop (to wake it up)
• Login (password = fsluser)
• Shut the laptop