UK Biobank

Brain Imaging Documentation

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documentation authors
Stephen Smith, Fidel Alfaro-Almagro and Karla Miller
Wellcome Centre for Integrative Neuroimaging (WIN-FMRIB), Oxford University on behalf of UK Biobank

Contributors to UK Biobank Brain Imaging

UK Biobank brain imaging scientific direction: Stephen Smith and Karla Miller (FMRIB, Oxford), Paul Matthews (Imperial).

Additional input on acquisitions/protocols/reconstruction/processing: Neal Bangerter (Brigham Young University, USA), Kamil Ugurbil, Essa Yacoub, Steen Moeller, Eddie Auerbach (CMRR, University of Minnesota, USA), Junqian Gordon Xu (Mount Sinai Medical Center, USA), David Thomas, Daniel Alexander, Gary Zhang, Enrico Kaden (UCL), Alessandro Daducci (EPFL, Switzerland), Tony Stoecker (Bonn, Germany), Stuart Clare, Heidi Johansen-Berg (FMRIB, Oxford), Deanna Barch, Greg Burgess, Nick Bloom, Dan Nolan, Michael Harms, Matt Glasser (Washington University St. Louis, USA), Doug Greve, Bruce Fischl, Jonathan Polimeni (MGH, USA), Andreas Bartsch (Heidelberg, Germany), Anna Murphy (Manchester), Fred Barkhof (VU Amsterdam, Netherlands), Christian Beckmann (Donders Nijmegen, Netherlands), Chris Rorden (University of South Carolina, USA), Peter Weale, Iulius Dragonu (Siemens UK), Steve Garratt (Project Manager, UK Biobank Imaging), Sarah Hudson (Lead Radiographer, UK Biobank Imaging).


IT/informatics: Duncan Mortimer, David Flitney, Matthew Webster, Paul McCarthy (FMRIB, Oxford), Alan Young, Jonathan Price, John Miller (CTSU, Oxford).

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1 Introduction

This documentation describes the brain imaging component of the UK Biobank prospective epidemiological study. It provides details of the acquisition protocols, image processing pipeline, image data files and derived measures (IDPs - imaging-derived phenotypes) of brain structure and function.

Researchers wanting to avoid reading the full technical detail relating to the imaging and image processing may wish to concentrate on Sections 1 and 4.

1.1 UK Biobank - background

UK Biobank is a prospective cohort study of over 500,000 individuals from across the United Kingdom. Participants, aged between 40 and 69, were invited to one of 22 centres across the UK between 2006 and 2010. Blood, urine and saliva samples were collected, physical measurements were taken, and each individual answered an extensive questionnaire focused on questions of health and lifestyle. The resource will provide a picture of how the health of the UK population develops over many years and it will enable researchers to improve the diagnosis and treatment of common diseases.

More recently, UK Biobank has collected genetic data on every participant. It has also begun to invite back some of the original participants for brain, heart and body imaging. It is the brain imaging that is the subject of this document.

The UK Biobank resource is open to the research community and it will grow and develop over time. It is a UK Biobank data access policy that findings that use UK Biobank data should be fed back to UK Biobank and made available to other researchers.

1.2 Referencing use of Brain Imaging Data

If you use UK Biobank brain imaging data in your research, you may want to cite:

- UK Biobank Brain Imaging Documentation.
  Stephen Smith, Fidel Alfaro Almagro and Karla Miller.
  http://biobank.ctsu.ox.ac.uk/crystal/docs/brain_mri.pdf
  (this document)

- Image processing and Quality Control for the first 10,000 brain imaging datasets from UK Biobank.
  NeuroImage 166(400–424), 2018.

- Multimodal population brain imaging in the UK Biobank prospective epidemiological study.

If you make use of the IDPs (summary measures described in more detail below, computed by the image processing pipeline), please do make this clear when describing the data and analyses. This will help with ongoing justification to funders for this component of UK Biobank.
1.3 UK Biobank Brain Imaging

Because of the very large numbers of study participants, the entire brain imaging protocol has to be completed within 35 minutes. Much effort has been made to optimise image quality given this strict limitation, and to achieve a suitable balance (of time/quality/robustness) between the different modalities acquired. To date the brain imaging data acquisition includes 6 modalities, covering structural, diffusion and functional imaging, with the order below reflecting the actual acquisition ordering:

- **T1**  A T1-weighted structural image. T1-weighted imaging is a structural technique with high-resolution depiction of brain anatomy, having strong contrast between grey and white matter, reflecting differences in the interaction of water with surrounding tissues (tissue T1 relaxation times). This modality provides IDPs primarily relating to volumes of brain tissues and structures. It is also critical for calculations of cross-subject and cross-modality alignments, needed in order to process all other brain modalities.

- **rfMRI**  Resting-state functional MRI timeseries data. Resting-state functional MRI measures changes in blood oxygenation associated with intrinsic brain activity (i.e., in the absence of an explicit task or sensory stimulus). Derived IDPs estimate the apparent connectivity between pairs of brain regions, as reflected in the presence of spontaneous co-fluctuations in signal (i.e., the appearance of a connection based on co-activity, as opposed to a structural tract from dMRI). Other IDPs reflect the amplitude of spontaneous fluctuation within each region.

- **tfMRI**  Task functional MRI timeseries data. Task functional MRI uses the same measurement technique as resting-state fMRI, while the subject performs a particular task or experiences a sensory stimulus. Derived IDPs relate to the strength of response to the specific task (or a specific component of a more complex cognitive process) within a given anatomical brain region. The task used in Biobank was chosen to engage a range of high-level cognitive systems.

- **T2_FLAIR**  A T2-weighted FLAIR structural image. T2-weighted imaging is a structural technique with contrast dominated by signal decay from interactions between water molecules (T2 relaxation times). Image intensity is primarily related to pathology, with relatively subtle signal differences between grey and white matter. T2 images depict alterations to tissue compartments typically associated with pathology (e.g., white matter lesions).

- **dMRI**  Diffusion MRI. Diffusion-weighted imaging is a structural technique that measures the ability of water molecules to move within their local tissue environment. Water diffusion is measured along a range of orientations, providing two types of IDPs. Local (voxel-wise) estimates of diffusion properties reflect the integrity of microstructural tissue compartments (e.g., diffusion tensor estimates). Long-range estimates based on tract-tracing (tractography) reflect structural connectivity between pairs of brain regions.

- **SWI**  Susceptibility-weighted imaging. Susceptibility-weighted imaging is a structural technique that is sensitive to magnetized tissue constituents (magnetic susceptibility). Data from one scan (including phase and magnitude images from two echo times) can be processed in multiple ways to reflect venous vasculature, microbleeds or aspects of microstructure (e.g., iron, calcium and myelin).

In addition to releasing raw data, an initial image processing pipeline has been run that has generated processed versions of the data, using publicly available image processing tools, primarily taken from FSL (the FMRIB Software Library [Jenkinson et al., 2012]). For example, the T1 structural image has been processed to remove non-brain parts of the image, and to segment the brain image into different tissue types. The pipeline has also been used to generate several QC (quality control) measures.

For most of the brain imaging modalities, the pipeline has also been used to generate many IDPs (image-derived phenotypes). These numerical pipeline outputs aim to be objective quantifications of different aspects of brain structure and function. IDPs range from simple gross measures, such as total brain volume, to very specific detailed measures, such as average functional connectivity between two specific brain regions. The goal is for IDPs to be useful summary measures derived from the imaging data, that can be used in analyses to relate to other non-imaging variables in UK Biobank, such as health outcome measures. Each IDP is presented as a separate data field within the UK Biobank showcase [http://www.ukbiobank.ac.uk/data-showcase](http://www.ukbiobank.ac.uk/data-showcase).

Over the coming months/years, the goal is to expand the analysis pipeline, including state of the art processing from a broader range of methods/models and software toolkits, where this will increase the quality, robustness and scope of processing applied and
IDPs generated. One high priority is to adapt the FreeSurfer / Human Connectome Project pipelines to achieve cortical surface modelling.

Some image data quality control (a combination of manual and automated checking) has taken place as part of the data processing; for example, IDPs are not generated for datasets that have been identified as being incomplete or very badly affected by artefacts. However, UK Biobank is committed to making available to researchers all imaging data acquired (see below for more details), and not just imaging datasets judged to be of very high quality. This is in part because different researchers may have different definitions of “acceptable quality”, and also because some researchers may want to develop their own processing pipelines to detect/correct image data quality problems. Therefore for any research carried out on the basis of the image data and IDPs, it is important to verify the quality of the datasets used in that research.

An email discussion list has been setup for researchers wanting to discuss any aspects of the UK Biobank brain imaging protocols, data and analysis: https://www.jiscmail.ac.uk/cgi-bin/webadmin?A0=UKB-NEUROIMAGING
2 Image Acquisition Protocols

This section describes the imaging hardware and acquisition protocols (in the order that the different modalities are acquired within the imaging session). The full protocol PDF (as auto-generated by the scanner) is provided at http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=2367; the most important protocol parameters are given below.

2.1 Brain imaging hardware

The scanner is a standard Siemens Skyra 3T running VD13A SP4 (as of October 2015), with a standard Siemens 32-channel RF receive head coil.

At this point all released data is from a single scanner dedicated to UK Biobank imaging, in Cheadle Manchester. In 2017 two further identical centres (in Newcastle and Reading) will begin scanning.

2.2 Echo-planar imaging

The EPI-based acquisitions (dMRI, rfMRI and tfMRI) utilize simultaneous multi-slice (multiband) acceleration [Larkman et al., 2001, Moeller et al., 2010]. Biobank uses pulse sequences and reconstruction code from the Center for Magnetic Resonance Research (CMRR), University of Minnesota https://www.cmrr.umn.edu/multiband. These developments were partially generated as part of the Human Connectome Project (HCP, NIH grant 1U54MH091657), as described in [Ugurbil et al., 2013].

The fMRI data and primary dMRI data are all acquired with AP (anterior-posterior) phase encoding direction.

Distortion correction of EPI requires an estimate of the static field map. This fieldmap is derived from pairs of spin-echo EPI acquisitions with opposite phase encoding directions, acquired as part of the dMRI dataset; in addition to the primary dMRI data, 3 b=0 images are acquired with reversed phase encoding for later fieldmap estimation (along with 3 b=0 images with standard phase encoding). The estimated fieldmap is used for distortion correction in both the dMRI and fMRI datasets. This approach was found to have similar accuracy to separate fieldmap acquisitions in much shorter time and with greater robustness against head motion.

2.3 Setup, shimming

Duration: 2 minutes

It is critical to achieve maximally consistent spatial coverage of scans in the presence of differences in subject positioning and head size. For each scan, the field-of-view is automatically determined based on Siemens’ auto-align software, which aligns a scout scan to an atlas. In the infrequent situation where auto-align failed, alignment was set by the radiographer.

T1 and T2 structurals are acquired using straight sagittal orientation (i.e., with the field-of-view aligned to the scanner axes). fMRI (task and resting-state), dMRI and SWI utilise slice angling to minimise the superior-inferior field-of-view, thus optimising volume acquisition speed. Using the population brain size and shape results from [Mennes et al., 2014], imaging matrix is angled such that the front of the brain is tilted down (relative to the imaging matrix) by 16°, with respect to the AC-PC line.

Shim field accuracy is critical for data quality, and was found to be suboptimal when using default settings on the MRI scanner, particularly for the simultaneous multi-slice EPI acquisitions. Initially, shim quality was improved by manually iterating the shimming process 3 times; this process which was later replaced by a single shim using a reduced shimming field-of-view, thereby improving resolution of the acquired field map. The scans are prescribed to avoid any subsequent re-shimming during the entire protocol.
2.4 T1-weighted structural imaging

Resolution: 1x1x1 mm  
Field-of-view: 208x256x256 matrix  
Duration: 5 minutes  
3D MPRAGE, sagittal, in-plane acceleration iPAT=2, prescan-normalise

The superior-inferior field-of-view is large (256mm), at little cost, in order to include reasonable amounts of neck/mouth, as those areas will be of interest to some researchers.

2.5 Resting-state functional MRI

Resolution: 2.4x2.4x2.4 mm  
Field-of-view: 88x88x64 matrix  
Duration: 6 minutes (490 timepoints)  
TR: 0.735 s  
TE: 39ms  
GE-EPI with x8 multislice acceleration, no iPAT, flip angle 52°, fat saturation

As implemented in the CMRR multiband acquisition, a separate "single-band reference scan" is also acquired. This has the same geometry (including EPI distortion) as the timeseries data, but has higher between-tissue contrast to noise, and is used as the reference scan in head motion correction and alignment to other modalities.

2.6 Task functional MRI

As for rfMRI, except:  
Duration: 4 minutes (332 timepoints)

The task is the Hariri faces/shapes “emotion” task [Hariri et al., 2002, Barch et al., 2013], as implemented in the HCP, but with shorter overall duration and hence fewer total stimulus block repeats. The participants are presented with blocks of trials and asked to decide either which of two faces presented on the bottom of the screen match the face at the top of the screen, or which of two shapes presented at the bottom of the screen match the shape at the top of the screen. The faces have either angry or fearful expressions.

The ePrime script that controls the video presented to the participant is derived from the one used by the HCP, and is available at http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=1462.

2.7 T2-weighted FLAIR structural imaging

Resolution: 1.05x1x1 mm  
Field-of-view: 192x256x256 matrix  
Duration: 6 minutes  
3D SPACE, sagittal, in-plane acceleration iPAT=2, partial Fourier = 7/8, fat saturation, elliptical k-space scanning, prescan-normalise

After early piloting, a standard T2/PD-weighted acquisition was dropped due to a combination of factors such as overall value and timing practicalities. However a T2-weighted FLAIR image is acquired, which is generally of good quality and which shows strong contrast for white matter hyperintensities.
2.8 Diffusion imaging

Resolution: 2x2x2 mm  
Field-of-view: 104x104x72 matrix  
Duration: 7 minutes (including 36 seconds phase-encoding reversed data)  
5x b=0 (+3x b=0 blip-reversed), 50x b=1000, 50x b=2000  
SE-EPI with x3 multislice acceleration, no iPAT, fat saturation  

For the two diffusion-weighted shells, 50 distinct diffusion-encoding directions were acquired (and all 100 directions are distinct). The diffusion preparation is a standard (“monopolar”) Stejskal-Tanner pulse sequence. This enables higher SNR due to a shorter echo time (TE=92ms) than than a twice-refocused (“bipolar”) sequence. This improvement comes at the expense of stronger eddy current distortions, which are removed in the image processing pipeline.

2.9 Susceptibility-weighted structural imaging

Resolution: 0.8x0.8x3 mm  
Field-of-view: 256x288x48 matrix  
Duration: 2.5 minutes  
Two echos, TE=9.42,20 ms  
3D, axial, in-plane acceleration iPAT=2, partial Fourier = 7/8, prescan-normalise  

To date the magnitude and phase images have been saved for each RF coil and echo time separately. In future the expectation is to combine these on the scanner.

2.10 Compatibility across different phases of imaging

Ideally the imaging protocol will stay fixed over time. However, early improvements in the dMRI and T2_FLAIR protocols were found to be very valuable, resulting in significant enough data improvements to outweigh the priority of holding things perfectly constant (and taking into account the relatively small numbers of datasets affected). This change was made at the start of protocol “Phase 3”; the different phases are described in detail below. A variable available in the UK Biobank database (Acquisition protocol phase) specifies which protocol phase (currently from 1 to 5) was used for a given subject.

2.10.1 Protocol Phase 1

Only 11 datasets were acquired within this initial phase, after which several major improvements were made in the protocol. None of these datasets were processed with the image processing pipeline to generate IDPs or processed imaging data.

2.10.2 Protocol Phase 2 (compared with Phase 3 and later)

Approximately 500 datasets were acquired with a protocol which, for dMRI and T2_FLAIR, are incompatible with later phases (i.e., are different from what is shown in the Siemens protocol PDF linked above). These differences are now described.

The Phase 2 T2_FLAIR scans did not use elliptical k-space coverage (which was used in later scans to reduce acquisition time with no significant loss in image quality), and used 6/8 partial-Fourier (instead of the later 7/8 partial-Fourier, a change which reduced image blurring in later scans with a small time penalty).

The Phase 2 dMRI scans used “bipolar” (twice-refocused spin echo) diffusion encoding, instead of the “monopolar” (Stejskal-Tanner single spin echo) approach used later. Recent advances in post-processing are able to remove the greater image distortions incurred by monopolar encoding, allowing a reduction in echo time from 112ms to 92ms, providing a substantial increase in SNR and reducing the TR from 4.06s to 3.6s, providing a large reduction in scan time. Other (more minor) differences in Phase 2 dMRI...
scans (compared with Phase 3) are: one fewer diffusion encoding direction per shell, a larger flip angle (93/180 instead of the later 78/160) and a greater number of blip-reversed b=0 images (5 instead of the later 3).

As described in more detail below, for these early “incompatible” scans, the raw T2_FLAIR and dMRI NIFTI images are available via the UK Biobank database, but have not been used in the full image processing pipeline, and do not have IDPs computed (as these would likely be incompatible with those generated later).

One final minor difference in the Phase 2 scans, which does not present incompatibility problems, is that the rfMRI and tfMRI protocols had additional timepoints (approximately 30s) compared with later scans.

2.10.3 Protocol Phase 4 (compared with Phase 3)

No significant changes were made between Phase 3 and 4. Three superfluous b=0 scans were removed. The T2_FLAIR was moved within the protocol to run after the fMRI scans. A new auto-shimming approach was put in place, with a reduced shimming field-of-view and fewer shim iterations; this saved time and was evaluated to result in very similar shimming quality. A small cross-hair was added to the video display, for subjects to focus on (except during tfMRI).

2.10.4 Protocol Phase 5

No significant changes; CMRR multiband software was upgraded to v12 (R012b).

2.10.5 Protocol Phase 6

No significant changes; CMRR multiband software was upgraded to R014.

2.10.6 Protocol Phase 7

No significant changes; CMRR multiband software was upgraded to R015.

2.10.7 Protocol Phase 8

No significant changes; Siemens scanner software was upgraded with service-pack SP7.
3 Image Processing Pipeline

In the near future the full image analysis pipeline scripts will be made available. At present the scripts primarily call tools from FSL, although the range of toolkits utilised will expand in future versions of the pipeline. For example, we plan to utilise FreeSurfer-based cortical surface modelling, in the context of running HCP-derived scripts for integrated cortical and subcortical/cerebellar modelling [Glasser et al., 2013].

3.1 Reconstruction of real-space data from k-space complex data

Images in the “real space” domain were reconstructed from the complex k-space domain in which data are collected. Unless otherwise specified, all images are signal magnitude.

Standard Siemens on-scanner conversion of complex multi-coil data was carried out for the T1 and T2_FLAIR data.

Image reconstruction for the simultaneous multi-slice EPI data (dMRI, rfMRI, tfMRI) was carried out using reconstruction software supplied by CMRR (available from the CMRR web site listed above).

SWI data has, to date, been saved as coil-separated real-space complex data, as it has not yet been possible to carry out appropriate multi-coil combination on the scanner for accurate reconstruction of phase images. This is expected to change in the near future.

3.2 Raw DICOM data conversion to NIFTI and download options

All real-space DICOM image files are converted to NIFTI format using Chris Rorden’s conversion tool dcm2niix https://github.com/rordenlab/dcm2niix. This tool also generates the diffusion-encoding b values and vectors files.

Image data is available from UK Biobank in both DICOM and (separately) NIFTI formats. Both forms include the raw (non-processed) data, the only differences being that the NIFTI-version T1/T2 structural images are defaced for subject anonymity (as described below), and the full multi-coil (pre-combination) SWI data is only available in the DICOM downloads. An individual zIfile download is for one modality from one subject for one data format (DICOM or NIFTI).

The NIFTI versions are the recommended option, partly because for each modality a small number of simply and consistently named images are provided (e.g., T1, rfMRI), as opposed to thousands of separate DICOM files (with complex naming conventions). Also, the NIFTI downloads, while overall only being 40% larger than pure-raw DICOM downloads, include not just the the raw images, but also images output by the processing pipeline, for example after gradient distortion correction (for all modalities), and correction for eddy currents and head motion (dMRI data), and artefact removal (rfMRI data).

3.3 Image anonymisation and raw DICOM data access

In order to protect study participant anonymity, the high resolution structural images (T1 and T2) are “defaced”. This involves setting voxels in the general regions of the face and ears to zero. This is achieved by estimating a linear transformation between the original data and a standard co-ordinate system (an expanded MNI152 template space), and back-projecting standard-space regions-of-interest into the native data, to allow for masking-out of the face/ears. Testing for overlap between (non-defaced) brain masks and the defacing masks shows only 8 subjects with any overlap at all, and all qualitatively show virtually no loss of brain voxels.

Hence in the NIFTI-format data released by UK Biobank, for the T1 and T2 data, only defaced versions are available (to protect anonymity of study participants). This matches common practice such as that in the HCP. The raw, non-defaced DICOM T1 and T2 data is classified as sensitive by UK Biobank; researchers requiring raw DICOM non-defaced T1/T2 data should contact UK Biobank to discuss this further.
3.4 Data/Folder file organisation

For each subject, the raw and processed imaging data files are organised into subfolders according to the different modalities (and described in more detail for each modality below).

When raw data is corrupted, missing or otherwise unusable, it is moved into a subfolder (inside the given modality’s folder) named unusable, and not processed any further (apart from defacing applied to the raw T1 and T2_FLAIR). This “unusable” data is included in the Biobank database, because some researchers may be interested in working with this data, for example, to develop new methods for detecting or even possibly correcting such data.

The evaluation of the T1 data for “usability” includes a rough manual review of all T1s (supplemented by a beta-version auto-QC approach) [Alfaro-Almagro et al., 2018]. Where a T1 is considered to have a serious problem it has been moved into the “unusable” subfolder as described above. This is for datasets where the issue is considered serious enough that the pipeline is unlikely to run well - which could be imaging artefacts/problems or very gross pathologies. More subtle pathologies that are subtle enough that we expect the pipeline to run OK are not treated as “unusable” in this way.

In the case of unusable T1 data, all other modalities’ raw imaging data are also considered unusable (because the pipeline cannot function without a usable T1). However, as with the T1 data, all such raw data is still available for download in the NIFTI packages (but without the pipeline processing applied).

In the case of the incompatible (Phase 2) dMRI and T2_FLAIR data (see above for protocol incompatibilities), these also are not processed with the image processing pipeline, but the raw data are moved to an incompatible folder, and available for download. For example, some researchers may wish to investigate the possibility of developing analyses which can handle the protocol incompatibilities.

3.5 Gradient distortion correction

Full 3D gradient distortion correction (GDC) is not available on the scanner for EPI data, and so all GDC is applied within the image analysis pipelines. Tools developed by the FreeSurfer and HCP teams are used for applying the correction, available at https://github.com/Washington-University/Pipelines. To run these tools also requires a proprietary data file from Siemens which describes the gradient nonlinearities (coeff.grad).

3.6 T1 processing

The raw original (defaced) T1-weighted structural image and other T1-derived pipeline outputs are in the folder T1.

The full FoV (field-of-view) raw T1 image, after defacing, is T1_orig_defaced. Apart from the defacing (and the fact that bias field has already been reduced via the on-scanner “pre-scan normalise” option), this is the raw T1 structural data, without any further processing such as gradient distortion correction.

The FoV is then cut down to reduce the amount of non-brain tissue (primarily blank space above the head and tissues below the brain), and GDC applied. Tools utilised to achieve this robustly include BET (Brain Extraction Tool [Smith, 2002]) and FLIRT (FMRIB’s Linear Image Regsitration Tool [Jenkinson and Smith, 2001, Jenkinson et al., 2002]), in conjunction with the MNI152 “nonlinear 6th generation” standard-space T1 template http://www.bic.mni.mcgill.ca/ServicesAtlases/ICBM152NLin6. This results in the reduced-FoV T1 head image T1.

The data is now nonlinearly warped to MNI152 space using FNIRT (FMRIB’s Nonlinear Image Registration Tool [Andersson et al., 2007b, Andersson et al., 2007a]), resulting in the warp transform file transforms/T1_to_MNI_warp_coef. A standard-space brain mask is then back-transformed into the space of the T1 (generating T1_brain_mask), and applied to the T1 image to generate a brain-extracted T1, T1_brain.

Next, tissue-type segmentation is applied using FAST (FMRIB’s Automated Segmentation Tool [Zhang et al., 2001]), with outputs in subfolder T1_fast. This provides a hard segmentation into CSF (cerebrospinal fluid), grey matter and white
matter (T1_brain_seg), as well as partial-volume images for each tissue type (T1_brain_pve_0, T1_brain_pve_1 and T1_brain_pve_2, respectively). This processing is also used to generate a fully bias-field-corrected version of the brain-extracted T1: T1_unbiased_brain.

These data are then used to carry out a SIENAX-style analysis (Structural Image Evaluation, using Normalisation, of Atrophy: Cross-sectional [Smith et al., 2002]). The external surface of the skull is estimated from the T1, and used to normalise brain tissue volumes for head size (compared with the MNI152 template). Volumes of different tissue types and total brain volume, both normalised for head size, and not normalised, are generated as IDPs and accessible from the UK Biobank database.

The FAST grey matter segmentation is also used to generate a further 139 IDPs, by summing the grey matter partial volume estimates within 139 ROIs. These ROIs are defined in MNI152 space, combining parcellations from several atlases: the Harvard-Oxford cortical and subcortical atlases https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases and the Diedrichsen cerebellar atlas http://www.diedrichsenlab.org/imaging/propatlas.htm. The previously estimated warp field (taking the subject’s data into standard space) is inverted and applied to the ROIs, to generate a version of the ROIs in native space, for masking onto the segmentation.

Subcortical structures (shapes and volumes) are modelled using FIRST (FMRIB’s Integrated Registration and Segmentation Tool [Patenaude et al., 2011]). The shape and volume outputs for 15 subcortical structures (in files *.bvars and *.vtk - see http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST/UserGuide) are stored in the T1_first subfolder. A single summary image, with a distinct integer value coding for each structure, is T1_first_all_fast_firstseg. The volumes of the different structures are saved as IDPs in the Biobank database.

3.7 T2_FLAIR processing

The original (defaced) T2-weighted structural image and other pipeline outputs are in folder T2_FLAIR.

The full FoV T2 image, after defacing, is T2_FLAIR_orig_defaced.

The T2 image is linearly aligned to the T1 using FLIRT, and the resulting transform is then combined with various transforms derived from the T1, in order to transform the T2 directly from the original space into both the individual subject’s T1 space and MNI standard space. By analogy with the T1-related images described above, this results in images T2_FLAIR and T2_FLAIR_brain, and a bias-corrected version of the latter T2_FLAIR_brain_unbiased (these being in the space of the T1), as well as T2_FLAIR_brain_to_MNI (MNI-space version).

The total volume of white-matter hyperintensities (WMHs, or white matter lesions) is estimated to generate an additional IDP. This is primarily utilising the T2_FLAIR data, but also the T1 data; this lesion segmentation is automatically carried out using the BIANCA tool[Griffanti et al., 2016].

3.8 SWI processing

The original SWI data and other pipeline outputs are in folder SWI. This data can provide a range of maps with distinct features related to magnetic susceptibility. Phase images have the potential to be used for quantitative susceptibility mapping, magnitude data can be used to calculate T2* relaxation rates and both magnitude and phase are used for generating venograms (see below) and for visualizing hemosiderin in microbleeds.

Combining phase images across coils requires care due to anomalous phase transitions in regions of focal signal dropout for a given coil. Currently, all coil channels are saved separately to enable combination of phase images in post-processing. Each coil channel phase image is first high-pass filtered to remove low-frequency phase variations (including both coil phase profiles and field distortion from bulk shape). A combined complex image is generated as the sum of the complex data from each coil (unfiltered magnitude and filtered phase), and the final phase image (filtered_phase) is the phase of this summation. Careful inspection of a small number of subjects found no anomalous phase transitions from individual channels in the final combined image.

Venograms (SWI) were calculated using an established reconstruction [Haacke et al., 2004], in which magnitude images are mul-
tiplied by a further filtration of the phase data to enhance the appearance of veins. The phase image is first thresholded (such that only paramagnetic susceptibility is non-unitary) and then taken to the fourth power to enhance contrast in veins. The chosen power represents a tradeoff between venous-tissue contrast and noise in the phase data.

R2* values were calculated from the magnitude data. First, a single magnitude image is calculated for each of the two echo times TE1 and TE2. This is calculated by taking the square of the magnitude image from each individual coil channel, summing across channels, and then taking the square root (typically referred to as “sum-of-squares” combination). The log of the ratio of these two echo time images (SOS_TE1 and SOS_TE2) was calculated, and scaled by the echo time difference, to give the R2*. T2* is calculated as the inverse of R2*. The T2* image is then spatially filtered (3x3x1 median filtering followed by limited dilation to fill missing data holes) to reduce noise (resulting in T2star), and transformed into the space of the T1 (via registration of the bias-field-normalised magnitude image SWI_TOTAL_MAG), the resulting image being T2star_to_T1.

3.9 B0 fieldmap processing

The B0 fieldmap-related pipeline outputs are in folder fieldmap (although these are derived primarily from the dMRI data).

All b=0 dMRI images with opposite phase-encoding direction (anterior-posterior (AP) and posterior-anterior (PA)) are analysed, to identify the highest-quality pair of AP and PA images. This optimal AP/PA pair is then fed into Topup http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TOPUP [Andersson et al., 2003] in order to estimate the B0 fieldmap and associated dMRI EPI distortions. GDC is then applied.

The EPI distortion information needed by the remaining dMRI processing is saved in files fieldmap_out_fieldcoef.nii.gz and fieldmap_out_movpar.txt.

The magnitude image is then linearly aligned to the T1, for later use in unwarping the fMRI data; the resulting transformation is applied to the fieldmap, resulting in the T1-space fieldmap fieldmap_fout_to_T1_brain_rad.

3.10 dMRI processing

The original dMRI data and processing pipeline outputs are in folder dMRI. The raw data is in folder dMRI/raw, which contains the primary data used for diffusion analyses (AP), along with associated b value and vector text files, and the 3 b=0 phase-reversed images (PA).

First the data is corrected for eddy currents and head motion, and has outlier-slices (individual slices in the 4D data) corrected, using the Eddy tool http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/EDDY [Andersson and Sotiropoulos, 2015, Andersson and Sotiropoulos, 2016]. GDC is then applied, resulting in the 4D output file dMRI/data_ud.

This is then fed into two complementary analyses, one based on tract-skeleton processing, and the other based on a richer modelling of within-voxel tract structure, followed by probabilistic tractography analysis (BEDPOSTx / PROBTRACKx). Both analysis streams then report a range of dMRI-derived measures within different tract regions: A) measures derived from diffusion-tensor modelling, and B) measures derived from microstructural model fitting. Outputs from both these modellings are in the dMRI subfolder.

The b=1000 shell (50 directions) is fed into the diffusion-tensor-imaging (DTI) fitting tool DTIFIT, creating DTI outputs such as fractional anisotropy dMRI/dti_FA, tensor mode dMRI/dti_MO and mean diffusivity dMRI/dti_MD.

In addition to the DTI fitting, the dMRI data is fed into NODDI (Neurite Orientation Dispersion and Density Imaging) modelling, using the AMICO (Accelerated Microstructure Imaging via Convex Optimization) tool https://github.com/daducci/AMICO [Zhang et al., 2012, Daducci et al., 2015]. This aims to generate meaningful voxelwise microstructural parameters, including ICVF (intra-cellular volume fraction - an index of white matter neurite density), ISOVF (isotropic or free water volume fraction) and OD (orientation dispersion index, a measure of within-voxel tract disorganisation).
3.10.1 TBSS-style analysis

The DTI FA image is then fed into TBSS (Tract-Based Spatial Statistics [Smith et al., 2006]), which aligns the FA image onto a standard-space white-matter skeleton, with alignment improved over the original TBSS skeleton-projection methodology through utilisation of a high-dimensional FNIRT-based warping [de Groot et al., 2013]. The resulting standard-space warp (TBSS/FA/dti_FA_to_MNI_warp) is applied to all other DTI/NODDI outputs. The final skeleton-space outputs are in TBSS/stats/all_*_skeletonised, where * represents each of the DTI and NODDI outputs (FA, etc). For each of the DTI/NODDI outputs, these skeletonised images are averaged across a set of 48 standard-space tract masks defined by the group of Susumu Mori at Johns Hopkins University [Mori et al., 2005, Wakana et al., 2007], similar to the processing applied in the ENIGMA project http://enigma.ini.usc.edu/protocols/dti-protocols.

3.10.2 Probabilistic-tractography-based analysis

Separately from the tensor/TBSS analysis, the Eddy output data is also fed into tractography-based analysis. This begins with within-voxel modelling of multi-fibre tract orientation structure via the BEDPOSTx tool (Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques) http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT/UserGuide followed by probabilistic tractography (with crossing fibre modelling) using PROBTRACKx [Behrens et al., 2003, Behrens et al., 2007, Jbabdi et al., 2012]. The BEDPOSTx outputs are in folder dMRI.bedpostX; for example, the posterior mean fractional voxel occupancy for the principle fibre is mean_f1samples and the posterior mean direction of this fibre is dyads1. The BEDPOSTx outputs are suitable for running tractography from any (voxel or region) seeding; the pipeline has already automatically mapped a set of 27 major tracts using standard-space start/stop ROI masks defined by AutoPtx http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/AutoPtx [de Groot et al., 2013]. Although the Eddy and BEDPOSTx outputs are in the space and resolution of the (GDC-unwarped) native diffusion data space, the nonlinear transformation between this space and 1mm MNI standard space (as estimated by TBSS above) is used to create tractography results in 1mm standard space. PROBTRACKx outputs are in autoptx_preproc/tracts. For each tract, and for each DTI/NODDI output image type, an IDP is generated - the weighted-mean value of the DTI/NODDI parameter within the tract (the weighting being determined by the tractography output).

3.11 rfMRI processing

The rfMRI data and processing outputs are in folder fMRI; the raw (original) timeseries data is rfMRI and the single-band (single timepoint) reference scan is rfMRI_SBREF.

The processed rfMRI data is in folder rfMRI.ica. The following pre-processing was applied: motion correction using MCFLIRT [Jenkinson et al., 2002]; grand-mean intensity normalisation of the entire 4D dataset by a single multiplicative factor; highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma=50.0s); EPI unwarping (utilising the fieldmaps as described above); GDC unwarping. Finally, structured artefacts are removed by ICA+FIX processing (Independent Component Analysis followed by FMRIB’s ICA-based X-noiseifier [Beckmann and Smith, 2004, Salimi-Khorshidi et al., 2014, Griffanti et al., 2014]). FIX was hand-trained on 40 Biobank rfMRI datasets, and leave-one-out testing showed (mean/median) 99.1/100.0% classification accuracy for non-artefact components and 98.1/98.3% accuracy for artefact components. The final pre-processed rfMRI timeseries data is filtered_func_data_clean. At this point no lowpass temporal or spatial filtering has been applied.

The EPI unwarping is a combined step that also includes alignment to the T1, though the unwarped data is written out in native (unwarped) fMRI space (and the transform to T1 space written out separately). This T1 alignment is carried out by FLIRT, with a final BBR cost function [Greve and Fischl, 2009]. After the fMRI GDC unwarping, a final FLIRT realignment to T1 is applied, to take into account any shifts resulting from the GDC unwarping. The previously described transform from T1 space to standard MNI space is utilised when fMRI data is needed in standard space.

A group-average RSN (resting-state network) analysis was carried out using 4100 datasets. First, each timeseries dataset was temporally demeaned and had variance normalisation applied according to [Beckmann and Smith, 2004]. Group-PCA output was generated by MIGP (MELODIC’s Incremental Group-PCA) from all subjects. This comprises the top 1200 weighted spa-
tial eigenvectors from a group-averaged PCA (a very close approximation to concatenating all subjects’ time series and then applying PCA) [Smith et al., 2014]. The MIGP output was fed into group-ICA using FSL’s MELODIC tool [Hyvärinen, 1999, Beckmann and Smith, 2004], applying spatial-ICA at two different dimensionalities (25 and 100). The dimensionality determines the number of distinct ICA components; a higher number means that the above-threshold regions within the spatial component maps will be smaller. The group-ICA spatial maps are available at http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=9028. The sets of ICA maps can be considered as “parcellations” of cortical and sub-cortical grey matter, though they lack some properties often assumed for parcellations - for example, ICA maps are not binary masks but contain a continuous range of values; they can overlap each other, and a given map can include multiple spatially separated peaks/regions. Any group-ICA components that are clearly identifiable as artefactual (i.e., not neuronally driven) are discarded during the network modelling described below; a text file is supplied with the group-ICA maps, listing the group-ICA components kept in the final network modelling.

For a given parcellation (group-ICA decomposition of D components), the set of ICA spatial maps was mapped onto each subject’s rfMRI time series data to derive one representative timeseries per ICA component (for these purposes each ICA component is considered as a network “node”). For each subject, these D timeseries can then be used in network analyses, described below. This is the first stage in a dual-regression analysis [Filippini et al., 2009]. The single-subject node timeseries are in subfolders rfMRI_*.dr (where * is the dimensionality).

The node timeseries are then used to estimate subject-specific network-matrices (also referred to as “netmats” or “parcellated connectomes”). For each subject, the D node-timeseries were fed into network modelling, discarding the clearly artefactual parcels (nodes), leaving D’ nodes. This results in a D’xD’ matrix of connectivity estimates. Network modelling was carried out using the FSLNets toolbox http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLNets. Network modelling is applied in two ways: 1. Using full normalized temporal correlation between every node timeseries and every other. This is a common approach and is very simple, but it has various practical and interpretational disadvantages including an inability to differentiate between directly connected nodes and nodes that are only connected via an intermediate node [Smith, 2012]. 2. Using partial temporal correlation between nodes’ time-series. This aims to estimate direct connection strengths better than achieved by full correlation. To slightly improve the estimates of partial correlation coefficients, L2 regularization is applied (setting rho=0.5 in the Ridge Regression netmats option in FSLNets). Netmat values were Gaussianised from Pearson correlation scores (r-values) into z-statistics, including empirical correction for temporal autocorrelation. Group-averagenetmatsareavailableat
http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=9028.

3.12 tfMRI processing

The tfMRI data and processing outputs are in folder fMRI; the raw timeseries data is tfMRI and the single-band (single timepoint) reference scan is tfMRI_SBREF.

The processed tfMRI data is in folder tfMRI.feat. The same pre-processing and registration was applied as for the rfMRI described above, except that spatial smoothing (using a Gaussian kernel of FWHM 5mm) was applied before the intensity normalisation, and no ICA+FIX artefact removal was run. The final pre-processed tfMRI timeseries data is filtered_func_data.

Task-induced activation modelling was carried out using FEAT (FMRI Expert Analysis Tool); time-series statistical analysis was carried out using FILM with local autocorrelation correction [Woolrich et al., 2001]. The timings of the blocks of the two task conditions (shapes and faces) are defined in text files custom_timing_files/ev1.txt and custom_timing_files/ev2.txt. 5 activation contrasts were defined (Shapes, Faces, Shapes+Faces, Shapes-Faces, Faces-_shapes), and an f-contrast also applied across Shapes and Faces.

The 3 contrasts of most interest are: 1 (Shapes), 2 (Faces) and 5 (Faces-Shapes), with the last of those being of particular interest with respect to amygdala activation. Group-average activation maps were derived from analysis across all subjects, and used to define ROIs for generating tfMRI IDPs. Four ROIs were derived; 1 (Shapes group-level fixed-effect z-statistic, thresholded at Z>120); 2 (Faces group-level fixed-effect z-statistic, thresholded at Z>120); 5 (Faces-Shapes group-level fixed-effect z-statistic, thresholded at Z>120); 5a (Faces-Shapes group-level fixed-effect z-statistic, thresholded at Z>120, and further masked by an amygdala-specific mask). The group-average activation maps and ROIs are available http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=9028.

The Featquery tool was used to extract summary statistics for the 3 main contrasts, for both activation effect size (expressed as a % signal change relative to the overall-image-mean baseline level) and statistical effect size (z-statistic), with each of these...
summarised across the relevant ROI in two ways - median across ROI voxels and 90th percentile across ROI voxels.

Display of the task video and logging of participant responses is carried out by ePrime software, which provides several response log files from each subject. These are not used in the above analyses (as the timings of the task blocks are fixed and already known, and the correctness of subject responses are not used in the above analyses), but are available in the UK Biobank database.
4 UK Biobank Database Variables

In addition to the raw and processed “bulk” image data files available from UK Biobank, there are a number of derived numerical measures available as standalone variables available in the database (i.e., these are summary numbers rather than images). This includes general information variables (such as imaging protocol Phase), QC (quality control) measures (such as overall signal-to-noise ratio for individual modalities) and IDPs (imaging-derived phenotypes, such as total brain volume and left hippocampus volume). These are now briefly described.

4.1 QC measures

All QC measures are designed such that “higher is worse”.

Several QC measures describe the “discrepancy” (generalised difference) between a given pair of images after they have been aligned together. Here a poor (large) score could arise either because the quality of the alignment is bad, or because one of the two images being compared is corrupted in some way. Two such QC measures quantitate the discrepancy between the T1 structural image and the standard (population average) template image - one after a linear alignment (which cannot correct for the fine-detailed differences between a given subject and the population average), and the other after a nonlinear alignment (which should achieve much better correspondence). Related to this, the overall amount of nonlinear warping necessary to achieve a detailed alignment to the standard template is summarised as one QC measure. Finally, several other QC measures describe the discrepancy between the T1 image (for a given subject) and each of the other modalities (for that same subject), after linear alignment of the other modalities to the T1.

Several other QC measures quantitate signal to noise ratio (SNR) in some of the modalities. For the T1, the tissue-type segmentation is used to estimate within-tissue-type noise level (standard deviation), as well as mean intensities for grey and white matter. These quantities are used to estimate overall image SNR and also CNR (contrast to noise - white-grey mean intensity difference normalised by noise level). In both cases these measures are inverted before being recorded as QC measures, so that “higher is worse”. From the preprocessed rfMRI (both before and after artefact removal) and tfMRI timeseries data, similar measures are calculated, but in this case the “noise” level is the temporal standard deviation. First, voxelwise SNR is calculated, and then the median (across brain voxels) estimated. This is then inverted for the reported QC measure.

Also from the rfMRI and tfMRI data, the total amount of head motion is summarised as additional QC measures. For each consecutive pair of timepoints, the mean displacement (averaged across the brain) is estimated, and this is then averaged across all timepoints.

Finally, from the dMRI data, the total number outlier slices (from all slices in all dMRI volumes) is reported, as output by the Eddy tool. This is mostly reflective of head motion during the dMRI scan.

4.2 IDPs

IDPs are designed such that each different IDP aims to describe one single objective and meaningful quantity in the brain imaging data, from simple global IDPs such as total brain volume, to highly specific, spatially-focal IDPs such as the mean white matter fractional anisotropy in the left uncinate fasciculus.

In general IDPs are not normalised for brain or head size (except for the few SIENAX measures that explicitly state that they are normalised in their summary descriptions). If it is desired to normalise an IDP for head size, the T1-based “headsize scaling factor” (http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=25000) should be used. Note that this is the scaling factor estimated when transforming from native to standard space, so to normalise variables for head size, one should multiply raw IDP values by this (not divide).

Other possibly useful confound variables include the summary fMRI motion variables, sex and age.

From the T1 structural image, several global volume measures are reported as distinct IDPs, both normalised for overall head size as well as not normalised: total brain (grey + white matter) volume; total white matter volume, total grey matter volume, ventricular
(non-peripheral) CSF (cerebrospinal fluid) volume; peripheral cortical grey matter volume. Also the overall volumetric head-size scaling factor is recorded as an IDP. The total “regional” grey matter volume is estimated in 139 different regions-of-interest defined from atlases in standard space. Finally, from the T1, several subcortical structures’ volumes (not normalised for brain/head size) are reported, in general with separate IDPs for left and right, such as left thalamus and right thalamus.

From the T2_FLAIR (combined with T1) data, white matter lesions are estimated, and an IDP is created as the total volume across all lesions.

From the SWI data, a T2* image is estimated. The median (across ROI voxels) T2* value is then estimated as a separate IDP for each of the subcortical structure ROIs (left thalamus, right caudate, etc.) estimated from the T1.

From the tfMRI data, activation is estimated for the 3 primary “contrasts” of interest (as described above). For these contrasts (“Shapes”, “Faces” and “Faces-Shapes”), a population-average activation was estimated and used to define a region-of-interest (ROI) within which to estimate subject-specific activation IDPs. Across voxels in the relevant ROI, the median and 90th percentile activation are estimated for each contrast, reporting both activation effect size (expressed as a % signal change relative to the overall-image-mean baseline level) and statistical effect size (z-statistic). The third contrast (“Faces-Shapes”) was also evaluated within an additional group-defined ROI - the intersection of the original group-average ROI for this contrast, and an amygdala mask derived from the Harvard-Oxford structural atlas.

From the rfMRI data, the group-average data was “parcellated” into areas at two different levels of detail (D=25 parcels spanning the brain and, separately, D=100). As described in more detail above, these parcellations were then mapped onto individual subjects’ datasets, and clearly-arteftactual parcels discarded, resulting in D’xD’ network models (matrices) for each subject. As the matrices are symmetric, only values above the diagonal are kept, and unwrapped into a single row of \((D' \times (D'-1) / 2)\) values per subject. This results in one “compound” IDP (containing all network matrix values for a given subject) for each original dimensionality (D=25 and 100) and for each network matrix estimation method (full correlation and partial correlation). Further IDPs are estimated as the fluctuation amplitudes (node temporal standard deviation) for each of the nodes, from both dimensionalities.

Spatially-specific IDPs related to the dMRI data are derived in two different ways, as mentioned above in the processing pipeline descriptions. All diffusion tensor imaging (DTI) measures (such as FA) and microstructural NODDI measures are summarised as averaged in specific areas/tracts. In the first set of measurements, the diffusion data is aligned to a white-matter tract skeleton, and the DTI/NODDI measures averaged within 48 distinct tract ROIs defined using the Johns Hopkins University tract atlas. In the second set of measurements, probabilistic tractography is run using a set of standard space seed/termination masks, and DTI/NODDI measures averaged within 27 distinct tracts’ maps.
References


A Glossary

**BOLD** Blood-oxygen-level dependent MRI contrast - the signal in fMRI that is sensitive to changes in oxygenation level in the blood, and hence a marker for local grey matter activation.

**z-statistic** a test statistic (e.g., Pearson’s r or t from a t-test) that has been transformed to be Gaussian (with mean 0, standard deviation 1) in the null scenario.

**T1** - the time constant defining the rate of recovery of magnetization (and therefore signal). Brain images with T1-weighted contrast exhibit strong contrast between grey and white matter and are useful for anatomical reference/analysis.

**T2** - the time constant defining the loss of magnetization (and therefore signal). Brain images with T2-weighted contrast are often used to identify white matter pathology, typically associated with high water content.

**T2** - a measure quantifying MRI signal decay that is enhanced (relative to T2) by microstructural compartments containing tissue constituents, such as iron or myelin, that are susceptible to magnetic fields.

**Diffusion tensor** - a description of how water diffusion is altered by the presence of tissue membranes. For example, water movement is strongly restricted perpendicular to white matter fibres but weakly along them, resulting in an elliptical diffusion tensor. See also: MD, FA, MO, L1,2,3 [Pierpaoli and Basser, 1996, Smith et al., 2015].

**FA** fractional anisotropy - a measure of white matter “integrity” derived from a diffusion tensor fit to dMRI data.

**MD** - mean diffusivity - the average strength of water diffusion, independent of direction.

**MO** - diffusion tensor mode - a discriminant between (e.g.) the presence of a single strong fibre in a voxel, vs multiple distinct fibres with different directions.

**L1,2,3** - in a diffusion tensor fit, the strength of diffusion along the principal axes of the ellipse (eigenvalues).

**ICVF** intra-cellular volume fraction - an index of white matter neurite density from NODDI modelling of dMRI data (Neurite Orientation Dispersion and Density Imaging [Zhang et al., 2012, Daducci et al., 2015]). Other NODDI modelling outputs include ISOVF (isotropic or free water volume fraction) and OD (orientation dispersion index, a measure of within-voxel tract disorganisation).
Figure 1: Pipeline flowcharts key.
Figure 2: Flowchart for the T1 processing pipeline.
Figure 3: Flowchart for the T1 defacing processing pipeline.
Figure 4: Flowchart for the T2_FLAIR processing pipeline.
Figure 5: Flowchart for the T2__FLAIR defacing processing pipeline.
Figure 6: Flowchart for the B0 fieldmap processing pipeline.
Figure 7: Flowchart for the B0 fieldmap mean magnitude image processing pipeline.
Figure 8: Flowchart for the overall fMRI processing pipelines.
Figure 9: Flowchart for the central parts of the fMRI processing pipelines.
Figure 10: Flowchart for the dMRI processing pipeline.