A brain imaging repository of normal structural MRI across the life course: Brain Images of Normal Subjects (BRAINS)

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ABSTRACT

The Brain Images of Normal Subjects (BRAINS) Imagebank (http://www.brainsimagebank.ac.uk) is an integrated repository project hosted by the University of Edinburgh and sponsored by the Scottish Imaging Network: A Platform for Scientific Excellence (SINAPSE) collaborators. BRAINS provide sharing and archiving of detailed normal human brain imaging and relevant phenotypic data already collected in studies of healthy volunteers across the life-course. It particularly focusses on the extremes of age (currently older age, and in future perinatal) where variability is largest, and which are under-represented in existing databanks.

BRAINS is a living imagebank where new data will be added when available. Currently BRAINS contains data from 808 healthy volunteers, from 15 to 81 years of age, from 7 projects in 3 centres. Additional completed and ongoing studies of normal individuals from 1st to 10th decades are in preparation and will be included as they become available.

BRAINS holds several MRI structural sequences, including T1, T2, T2* and fluid attenuated inversion recovery (FLAIR), available in DICOM (http://dicom.nema.org/); in future Diffusion Tensor Imaging (DTI) will be added where available. Images are linked to a wide range of 'textual data', such as age, medical history, physiological measures (e.g. blood pressure), medication use, cognitive ability, and perinatal information for pre/post-natal subjects. The imagebank can be searched to include or exclude ranges of these variables to create better estimates of 'what is normal' at different ages.

Introduction

What is our imagebank designed to do?

The Brain Images of Normal Subjects (BRAINS) Imagebank (http://www.brainsimagebank.ac.uk) is designed to provide detailed brain imaging data of healthy/'normal' individuals across the human life-course. The imagebank is a searchable database of integrated data sets already collected as part of research studies which include healthy (or control) subjects. These studies include detailed MRI using a range of sequences, and associated data, e.g. demographic details, health, and cognitive tests, and pregnancy details (for perinatal subjects). A key strength of BRAINS is the range and detail of these non-imaging variables. We are initially focussing on collating data from imaging studies at the extremes of life (old age, and later, perinatal) where least data are available in other databanks and there is most variability in brain structure (Serag et al., 2012; Sowell et al., 2003; Dickie et al., 2012a; Dickie et al., 2015a), but our imagebank includes subjects of all ages.

The definition of 'normal' is not simple and therefore this imagebank can be searched by associated data such as, blood pressure, body mass index, cognitive test scores, gestational age at birth. For example, hypertension is so prevalent in older people that it can be regarded as normal, but some investigators may wish to study participants with blood

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pressure within a certain range, and/or by imaging parameters such as the degree of atrophy or white matter lesions, that can vary widely in normal people with age. Brain structure in infancy is commonly altered in association with preterm birth, but not all preterm infants develop impairment, which leaves uncertainties about what is 'normal' in early life (Boardman et al., 2007, 2010). The imagebank will be expanded in the future to include new data as they become available, and subjects from other geographical locations.

The availability of data including clinically relevant MRI sequences from healthy volunteers across the life-course (linked with related phenotypical, demographic and cognitive measures), without diagnosed disease is an essential resource:

(i) As a reference atlas, for interpretation of brain images in clinical diagnosis, such as having access to healthy subject reference images closely matched to a patient's age and linked data (e.g. hypertension, diabetes), to improve diagnostic accuracy (Farrell et al., 2009), and

(ii) To develop new methods to detect brain pathology and associated clinical manifestations, such as early markers of neurodevelopmental impairment or dementia (Dickie et al., 2015a, b).

We will build and share developmental ranked atlases across the life-course, similar to child growth charts, but for the brain (Dickie et al., 2013, Dickie et al., 2015a). The imagebank will provide multiple data sets that can be used to test the accuracy and reproducibility of image processing methods and algorithms, in clinical and research settings. It will aid in determining early markers of disease by defining boundaries of normality to provide more precise estimates of disease risk. The reuse of data from already-funded primary studies is encouraged to increase value and reduce waste in research (http://researchwaste.net/).

The BRAINS Imagebank is hosted by the Brain Research Imaging Centre at Edinburgh University, Scotland, UK on behalf of a Steering Committee which includes the Principal Investigators of the original studies, experts in ethics, law and governance, and lay representatives (http://www.brainsimagebank.ac.uk/steering). The BRAINS datasets are from previously funded and ongoing studies by members of the Scottish Imaging Network, A Platform for Scientific Excellence (SINAPSE), namely the universities of Aberdeen, Glasgow, Dundee, St Andrews, Stirling, and Edinburgh. It is funded by the Brain Research Imaging Centre at Edinburgh University, SINAPSE (http://www.sinapse.ac.uk/), BBSRC Sparking impact (http://www.bbsrc.ac.uk/), and Edinburgh & Lothians Health Foundation (ELHF, http://www.elhf.co.uk/).

Background: comparison with existing brain image databanks

In our systematic review of existing structural brain image databanks, including OASIS, ADNI, UK Biobank, and IXI among others, we found that normal subjects older than 60 years were relatively underrepresented and that these subjects often had limited cognitive and medical metadata to support their classification as 'normal' (Dickie et al., 2012a, b). These subjects were mainly recruited as controls in studies of dementia, e.g. OASIS and ADNI, and their classification as 'normal' was generally determined through dementia-based assessments, e.g., clinical dementia rating (CDR) and Mini-Mental Statement Examination (MMSE). The majority of these subjects were aged between 70 and 79 years. Further, there were a limited range of sequences available for many of these subjects, e.g., only T1 images are provided in OASIS. Fluid attenuated inversion recovery (FLAIR) images, required to effectively classify white matter hyperintensities (Wardlaw et al., 2013), were often not available in other Banks (Dickie et al., 2012a, b). BRAINS is unique among existing image banks in including a) a wide range of sequences for most subjects (e.g., T1, T2, T2*, and FLAIR), b) a

focus on normal subjects aged over 60 years, up to the tenth decade (and in future perinatal subjects) and c) an extensive battery of cognitive and medical results in subjects often specifically recruited for studies of 'normal' cognitive ageing.

Materials and methods

The architecture underlying the BRAINS imagebank is based on the Extensible Neuroimaging Archive Toolkit (XNAT) (https://wiki.xnat.org/, Marcus et al., 2007). A key reason for adopting the XNAT platform was the extensibility of its data model. The BRAINS imagebank delivers two alternative web interfaces. The primary interface is the 'Guest' web application interface, which is provided for external users, delivered via Apache Tomcat. The secondary interface is the default XNAT interface and is only available to the BRAINS project team and collaborators (PIs of hosted projects), to allow for access control, data curation and quality control. The 'Guest' interface allows searching of the anonymised data using imaging and associated data fields, and the option to save a search for later use.

Data quality control

Details of the protocol and quality control processes of the contributing projects will be provided where possible (http://www.brainsimagebank.ac.uk/datasets). This varies between studies and centres. Data from regular phantom scanning is available for all scanners (e.g. the Quality Assurance procedures of the Edinburgh Brain Research Imaging Centre http://www.sbirc.ed.ac.uk/research/qualityassurance/qualityassurance.html). Details of individual studies image analysis and data checking QC are provided in individual linked publications. In addition, all data are checked during import into BRAINS, both image (sequence details, completeness of scan) and demographic data (matching of IDs to images, completeness of variables, variables range and definitions) — see 'data cleaning' below.

Exclusion criteria

Imaging: All individual studies require scans to be reported by a clinical neuroradiologist, and anyone with a scan which would represent significant pathology (e.g. cystic periventricular leukomalacia, cerebral haemorrhage or large infarct, perinatal stroke, or large tumour such as pituitary adenoma or glioma) would be excluded, but the presence of incidental abnormalities, e.g. white matter lesions, small infarcts or microhaemorrhages, that are common accompaniments of ageing and which were not associated with any clinically evident impairment, would be included. These features are reported in the database.

Clinical: All subjects are identified as 'healthy' or 'normal' when recruited for the original studies. References to the original studies are included in the data provenance, but in general people are living independently in the community, without severe physical, psychiatric or neurodegenerative disease that impacts on their daily life. Some are control groups for studies of disease. Acknowledging the wide range of 'normality', we include people with conditions common in older age — e.g. diabetes, hypertension — but record this so that these parameters can be included or excluded by users. People with low MMSE may have been excluded by the original studies, but BRAINS has not excluded any subjects based on MMSE scores (or other cognitive test scores where included in the original studies and provided to BRAINS).

BRAINS imagebank architecture

The BRAINS imagebank is created using two support databases (Fig. 1). The first database, the 'link' database, holds a linking table to enable a secure ID mapping service, for linking of new data sets to existing sets (e.g. identifying subjects with multiple visits), and for reverse
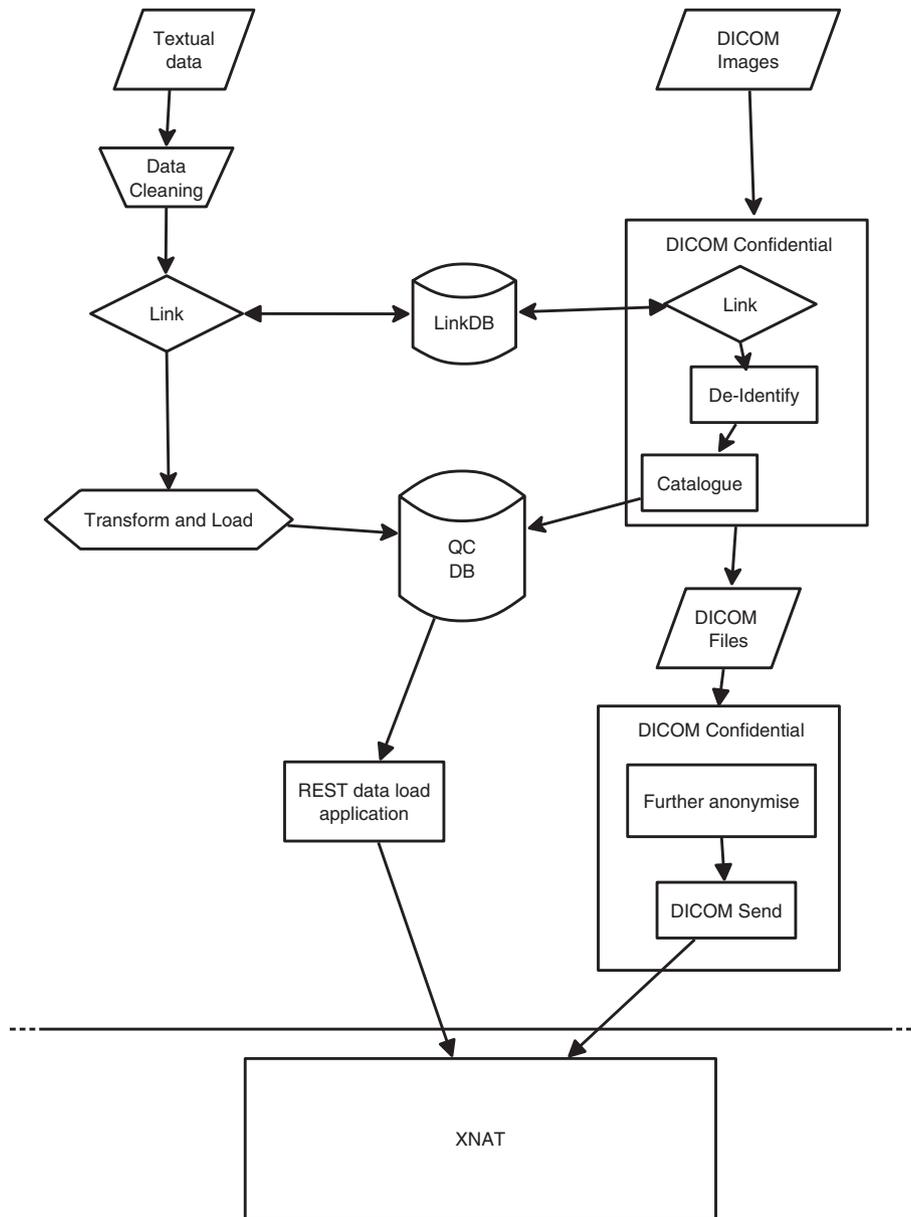
Fig. 1. Multi-stage data extraction, transformation and load (ETL). 'Textual data' — all non-image data: clinical, phenotypic, demographic, lifestyle and cognitive measures.

linking anonymised data should the need arise. Longitudinal data for a specific subject will have the same subject ID, with a separate visit ID.

Initially, the Textual Data pass through 'Data Cleaning' (Fig. 1). This involves checking the formats, coding, and ranges of textual data, and converting where necessary to fit the BRAINS schema.

The purpose of the second database, the 'Quality Control' (QC) database (MySQL), is to ensure QC for imaging, data linkage, and anonymisation. It contains data from the DICOM images and medical and related information from the original projects. The database is divided into tables corresponding to two main blocks depending on the origin: DICOM or other. The data are de-identified, but with a relatively low level of anonymity (i.e. name and patient ID removed). The textual data in the DICOM images is anonymised and catalogued using DICOM Confidential (Rodríguez González et al., 2010). The link and QC databases are stored on a secure server on our internal network, with strict access restrictions.

QC tasks include:

- Physical units homogenisation (e.g. magnetic field in Tesla).
- Values codification/concept mapping (e.g. sequence types 'FSE T2'/ 'T2').
- Inspection of "abnormal" values.

Anonymisation protocol

The original projects contributing data to the BRAINS imagebank often involve Person Identifiable Data (PID). Data available in the BRAINS imagebank are anonymised, and checked for anonymity.

The 'link database' contains a series of tables providing mappings from the original patient IDs and subjects' study IDs to their assigned BRAINS subject ID (BID). The BID is a randomly generated ID following

the pattern "BIDxxxxx" where x is a digit. It uses the Java random number generator (48-bit seed, which is modified using a linear congruential formula). We also check for collisions with previously generated BIDs.

These BIDs are generated when data for a new subject are processed for their inclusion in the QC database. The mapping between the original ID and the generated BID is stored in the 'link database' in order to ensure that longitudinal data are assigned to the correct BID.

The DICOM images are anonymised in a multi-stage process. Firstly, basic DICOM de-identification is performed for loading the data into the QC database. This removes the most obvious identifiers like the person's name, and patient ID, and removal of all private tags and rejection of DICOM images with information burned into the pixel data. The patient ID is substituted by the BID. This step is performed by DICOM Confidential and includes the generation of the DICOM catalogue tables in the QC database.

Further and much stricter DICOM de-identification is performed, again using DICOM Confidential (Rodríguez González et al., 2010), before sending the DICOM images to the BRAINS imagebank. The privacy policy in this case is based on the DICOM standard basic profile with the 'keep longitudinal information' option. This includes removal of attributes like the date of birth, information about the institution and staff involved in the scanning, and substitution of the UIDs.

Face de-identification is performed by the removal of distinguishing features from the image: face, teeth, ears etc. (Bischoff-Grethe et al., 2007), and the results visually checked.

Standardisation of textual data

Some adjustments are made to raw data to avoid possibility of re-identification, e.g. 'age' is rounded to nearest year (excepting infant data), dates of scans are removed but the ordering is preserved for longitudinal data. A complete list of data mapping transformation information is available from the BRAINS web site (http://www.brainsimagebank.ac.uk/userguide).

BRAINS schema

The BRAINS schema covers the range of imaging and associated data in each included study. Not all studies collect or provide all associated data. To implement the BRAINS schema XNAT data types were enriched and specialised by child data types specified in XML Schema documents.

The initial release of BRAINS will be searchable by a core subset of the schema fields. As the BRAINS imagebank is developed we will extend the searchable subset to cover the complete set of schema fields. A data dictionary of the non-imaging data included can be found at http://www.brainsimagebank.ac.uk/datadictionary and a summary of all current data can be found at http://www.brainsimagebank.ac.uk/subjectQuery/summary.

The complete BRAINS schema covers the following broad categories:

Demographics e.g. Age at data collection time; occupation; education
Measurements e.g. Blood pressure; weight; height
Medical history e.g. Perinatal details; prior head trauma; diabetes
Medications e.g. number of medications; any anti-platelet; statin; anti-hypertensive; antidepressant
Risk factors e.g. Smoking; family history of stroke
Clinical data — Scan findings, e.g. brain volume; white matter lesions — Fazekas score (Fazekas et al., 1987)
Clinical data — Cognitive tests, e.g. Hospital Anxiety and Depression Scale (HADS) – depression;
Image acquisition e.g. imaging protocol information
Image DICOM data e.g. Information from the DICOM headers
Image processed data e.g. Co-registered data

A major issue in combining these heterogeneous datasets is how to combine Textual data which may be recorded in different ways (e.g. age as whole years, months, weeks or days, or in decimal format), measured in different ways (e.g. blood pressure using an automated or manual sphygmomanometer) or using different tests to measure the same construct e.g. National Adult Reading Test (NART) or Mill Hill test for vocabulary/crystallised ability. An ontologist working with domain experts creates mappings from the original dataset to the BRAINS schema, and all decisions are recorded. Missing data are coded as 'not available'. Details of how we standardised the format of textual data will be available on our website once standardisations are finalised. The current (human readable) Textual data schema can be found at http://www.brainsimagebank.ac.uk/datadictionary, and (xml format: http://sourceforge.net/projects/ brainsimagebank/). We have a protocol which is provided to PIs of new studies to facilitate the collection of new BRAINS data as part of their study design, based on our core Textual data schema.

Governance

The BRAINS steering committee is comprised of the BRAINS Imagebank management team, Principal Investigators (PIs) of included studies, legal and ethical experts and lay representatives. BRAINS has ethical approval for anonymous use of data from the West of Scotland Research Ethics Committee (http://www.nhsggc.org.uk/about-us/professional-support-sites/research-development/west-of-scotland-research-ethics-service/), to whom we will provide annual reports of all activity, including a risk register and a record of any serious adverse events.

Registration, data access and user validation

User account registration
Initially users seeking access to the imagebank must complete an automated registration form (http://www.brainsimagebank.ac.uk/register). This allows access to the BRAINS imagebank Guest web interface. The Guest interface has a simple search page which allows users to query the BRAINS imagebank, and save queries. We are currently piloting the beta version of the Guest web interface and will amend the search interface and display in response to feedback. The search fields available in the current version are given in Table 1.

Running a search produces a summary of the relevant data, e.g. mean, range, standard deviation.

Data access request and data usage agreement

Once the user has identified the data of interest they can submit a project proposal to the BRAINS imagebank with a 'Data Access Request form' (http://www.brainsimagebank.ac.uk/dataRequest). The user's identity will then be validated by establishing a valid link between the user and their organisation. Both imaging and associated data should be requested together, preferably with a saved query. The proposal

Table 1
Currently available search fields in the BRAINS imagebank.

Field	Description
Age range	Age at data acquisition
Sex	M/F/Unknown
Handedness	Right/Left/Ambidextrous/Unknown
Sequence types	T1, T2, T2*, T1 GRE, FLAIR
Systolic blood pressure	mmHg
Diastolic blood pressure	mmHg
MMSE score	Mini Mental State Examination
Exclude any of	Stroke, hypertension or diabetes
Only include subjects with known	Occupation/years of formal education/smoking status/alcohol use

will be considered by the BRAINS Steering Committee by seeking active agreement by at least 3 members, and no disagreement by any member, with a target for decision within 5 working days. The proposal will be evaluated against the BRAINS ethical agreements. If the proposal is judged to accord with those agreements and represents an appropriate usage of the data according to principles agreed by the Steering Committed, then a "Data Usage Agreement" will be made, and lastly the BRAINS data managers will provide the user with access to the specified data. Users are encouraged to return copies of any derived data to the BRAINS imagebank. This process will be reviewed, and can be amended by agreement with the Steering Committee.

Downloading data

Data is provided from a separate server in compressed downloadable packages containing image formats in DICOM, and textual data in CSV. These packages will have the image sequences bundled in a per-subject per-project manner to facilitate the transfer of large data sets, by Datasync (http://www.ed.ac.uk/information-services/computing/desktop-personal/datasync).

Users of BRAINS imagebank data should be aware that combining MRI scans from multiple protocols, scanners or sites can influence the design of their experiments (Zhu et al., 2011, Jovicich et al., 2006). We are adding data from phantoms at different sites to allow quantification of these differences. We are adding the data from the Calibrain study (Gountouna et al., 2010), a prospective multi-site harmonisation study with human and imaging phantoms from three sites.

Revisions and withdrawals

There is a mechanism for informing existing users of data that has been withdrawn, but we do not have the means to support this service at this time. Users will be notified of new or updated data sets in the BRAINS imagebank as they become available.

We request that users of data inform us of publications, and acknowledge the use of data from BRAINS. We also request that they supply a list of the actual data used (if not the full set of variables requested) to facilitate replication of results and testing of methods.

Results

Image and Textual data collection

What is available? Data currently in the BRAINS image bank:
The BRAINS imagebank currently consists of data from 808 healthy volunteers, age range: 15–81 years, spanning seven previously funded projects. This is a living imagebank, with new data added when available. The current summary of included data is at http://www.brainsimagebank.ac.uk/subjectQuery/summary. These pseudo anonymised data sets contain a range of structural MRI sequences, including T1, T2, T2*, FLAIR, in DICOM format, and a range of associated data, e.g. perinatal details and sex (for neonatal data), blood pressure, age, Mini Mental State Examination (MMSE) (in CSV format). The associated data are too extensive to list here: see section on 'BRAINS schema' above.

Simpsons Study (Shenkin et al., 2009): This study contains n = 111 subjects aged 75–81 years with MRI sequences T2, T1, T2*, FLAIR at 1.5 T and detailed demographic, physical and cognitive measures. The study was funded by the Medical Research Council Clinical Training Fellowship to Susan Shenkin (www.mrc.ac.uk), and Chest Heart & Stroke Scotland (www.chss.org.uk).

Aberdeen Birth Cohort (Whalley et al., 2011a): The study contains n = 244 subjects aged 77–80 years with MRI sequences T2, T1, FLAIR at 1.0/1.5 T and detailed demographic, physical and cognitive measures. (http://www.abdn.ac.uk/birth-cohorts/1936/). The study was funded by The Engineering and Physical Sciences Research Council; Pump

Priming Grant Scheme (www.rcr.ac.uk/pump-priming-grant-scheme), Tenovus Scotland, SINAPSE, Pfizer, TMVS, Varian, GE healthcare, Siemens, GSK, ReNeuron, LUX Innovate, Propeller, NHS R&D, SHIL, SFC SPIRIT, Alzheimer's Research UK.

Psychological, social and biological determinants of ill health (pSoBid) in Glasgow: A cross-sectional, population-based study. Funded by The Glasgow Centre for Population Health (2013) (Krishnadas et al., 2013 and McLean et al., 2012) which is a partnership between NHS Greater Glasgow and Clyde, Glasgow City Council and the University of Glasgow, supported by the Scottish Government. The study contains n = 45 subjects aged 20–60 years with MRI sequences T2, T1 at 3.0 T and detailed demographic, social, physical and cognitive measures.

Amygdala 2 study (Hall et al., 2007): This study contains n = 55 control subjects aged 19–60 years with MRI sequences T2, T1 at 1.5 T and demographic information and cognitive testing. This study was funded by Stanley Medical Research Institute (www2.stanleyresearch.org), and the Sir Mortimer and Theresa Sackler Foundation (opencharities.org/charities/1128926).

NIH DTI study (Dickie et al., 2015a, b): The contributed data contains n = 80 Control subjects aged 25–65 years with MRI sequences T2, T1, T2*, FLAIR (DTI to be added) at 1.5 T, demographic information, brief medical history and cognitive testing. This study was funded by the National Institutes of Health grant R01 EB004155-03.

Bipolar Family Study (Whalley et al., 2011b; Sprooten et al., 2011): The contributed data contains n = 224 Control subjects aged 15–28 years with MRI sequences T1, T2, DWI at 1.5 T.

Glasgow 45 Healthy Volunteers (http://theses.gla.ac.uk/id/eprint/3133): The contributed data contains n = 45 control subjects aged 19–64 years, years with MRI sequences FLAIR, T2, T1 at 3 T and basic demographic details.

Studies pending submission will increase the number of subjects in the following age ranges, all include current and premorbid cognition, medical information and demographics: neonatal (n ≈ 250), 20–60 years (n ≈ 120), 65–75 years (n ≈ 100), 72–79 years (n ≈ 750), 90 years (n ≈ 50), with others in the 40–80 year age range currently being scanned.

Discussion and future work

The BRAINS imagebank is a living imagebank, meaning that it will include more data, with a further 1607 existing sets of data planned for immediate inclusion, spanning nineteen projects. Further data from ongoing and future studies with healthy volunteers will be included when it becomes available. For example, an estimated 3000 new healthy volunteers spanning a range of ages from 1st to 7th decades will be included over the next five years from studies in Scotland, giving over 5000 subjects by the year 2020. We will also link with other initiatives, e.g. in the Dementias Platform UK (http://www.mrc.ac.uk/research/facilities/dementias-platform-uk/) to maximise opportunities to increase sample size in meta-analyses of early dementia risk.

Due to the inclusion of heterogenous studies, we provide as much provenance data (http://www.brainsimagebank.ac.uk/datasets) as possible for each data set, e.g. recruitment methods, exclusion criteria, original study purpose, geographic area, ethics, and consent form. Citable Digital Object Identifiers (DOIs)/Uniform Resource Identifiers (URIs) will be included for each available dataset. Principal Investigators (PIs) who contribute data will complete a data contribution agreement (http://www.brainsimagebank.ac.uk) and provide provenance data including links to original publications describing the study. PIs only provide data that they agree can be shared, e.g. once primary analyses are complete. They are not obligated to provide all variables from their study. Lastly, we will provide processed and analysed data, primarily to support the creation and use of statistical reference models, brain templates and reference atlases (e.g., Dickie et al., 2012b, 2013, 2014, 2015a, 2015b). Data are provided to BRAINS from the original study Principal Investigators, with federation where possible to allow

comparison between similar variables. Data provenance and subsequent data harmonisation is described for all variables (http://www.brainsimagebank.ac.uk/datadictionary). No cross-site standardisation of imaging or non-imaging data was performed, with the exception of CaliBrain (Gountouna et al., 2010), a multicenter harmonisation study. BRAINS represents a post-hoc data repository, to facilitate the use and re-use of previously collected data, which will contribute to increased value and reduced waste in imaging research (Macleod et al., 2014).

Contributors

Our current ethics agreement for data contribution covers projects from Scotland. If this is extended to other countries then the different legal and ethical frameworks will need to be considered.

Long term plan

Long term management and maintenance is currently supported by the Brain Research Imaging Centre at the University of Edinburgh, until substantive funding can be secured. New data and follow up data will be added to the imagebank when it is available e.g. we estimate 3000 new subjects by 2020. We encourage feedback and collaboration.

Acknowledgments

Conflicts of interest

The authors have no conflicts of interest to declare in relation to the current work.

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