Lifebrain

D3.2. Tool for post hoc harmonization of MRI data across sites

Project title:	Healthy minds from 0 to 100 years: Optimizing the use of European brain imaging cohorts
Due date of deliverable:	30th September, 2017
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Leader for this deliverable:	University of Oslo

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Final evaluation	Anders M. Fjell	UiO	WP6 leader
	Barbara B. Friedman	UiO	Administrative coordinator

Document History				
Release	**Date**	**Reason for Change**	**Status (Draft/In-review/Submitted**	**Distribution**
1.0.	12.09.2017	First draft sent for the travelling brain coordinator team	Sent for commenting	OneDrive
2.0.	19.09.2017	Revised version	Internal evaluation	OneDrive
3.0.	28.09.2017	Final version	Final revision	Participant portal

Dissemination level		
PU	Public	**X**
PP	Restricted to other programme participants (including the Commission Services)	
RE	Restricted to a group specified by the consortium (including the Commission Services)	
CO	Confidential, only for members of the consortium (including the Commission Services)	

Executive summary

The LB consortium is aware of the problems of multi-site scanning and is engaged in an effort to address this problem. Therefore, Task 3.2. has been included in the LB proposal.

Task 3.2: Development and validation of a posteriori harmonization of MRI data. Lead: UiO; Participants: UOXF, REGIONH, UiO, MPIB (M1-M9)

The deliverable of this task is D3.2. Tool for post hoc harmonization of MRI data across sites, to allow integration of data from different scanners/sites.

8 sites are contributing data in Lifebrain, with different scanners and sequences. These differences would affect our MRI-derived measures. For all sites except UOXF, scanners used to collect at least some of the data that will feed into Lifebrain still exist, making it possible to send a selection of "brains" around in the Lifebrain consortium to get an idea of the between scanner effects.

Therefore, a "travelling brain tour" was organized with two objectives:

- Get a measure of within and between-scanner variability in Lifebrain
- Possibly work on methods to reduce between-scanner variance

In the summer of 2017, 7 volunteers have been scanned at 7 Lifebrain sites, on 11 LB scanning machines.

Based on data from the 7 participants across all Lifebrain scanners it becomes possible to generate atlas-based intensity transformations and B1-bias fields which then would be used to correct for scanner differences.

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List of acronyms/ abbreviations

Lifebrain	Healthy minds from 0-100 years: Optimizing the use of European brain imaging cohorts
EB	Executive Board
LB	Lifebrain
MPIB	Max Planck Institute, Berlin
MRI	Magnetic Resonance Imaging
REGIONH	Region Hovedstaden
UB	University of Barcelona
UCAM	University of Cambridge
UCAM (MRC-CBU)	Medical Research Council Cognition and Brain Sciences Unit at the University of Cambridge
UiO	University of Oslo
UmU	Umeå Universitet
UOXF	University of Oxford
VUmc	University Medical Center Amsterdam
WP	Work Package

Introduction

Deliverable description

D3.2. Tool for post hoc harmonization of MRI data across sites, to allow integration of data from different scanners/sites

Task 3.2: Development and validation of a posteriori harmonization of MRI data. Lead: UiO; Participants: UOXF, REGIONH, UiO, MPIB (M1-M9)

The task will implement and test a novel procedure to correct images for scanner specific differences in tissue contrast and intensity non-uniformity. We will arrange for a smaller number of pilot participants to be scanned at all scanners and sites providing MRI data to allow quantification of possible between-site and between-scanner differences. Implementation and testing of this correction procedure in Lifebrain will allow more accurate calculations from scans acquired with different scanners or parameters and will represented a central aspect of subsequent harmonization of LifeBrain MRI data.

Objective of deliverable

Implement and test a novel procedure to correct images for scanner-specific differences in tissue contrast and intensity non-uniformity.

Task 3.2. in practice

In Lifebrain we have 8 sites contributing data to the Lifebrain database, with different scanners and sequences. These differences will affect our MRI-derived measures. For all sites except UOXF, scanners used to collect at least some of the data that will feed into Lifebrain still exist, making it possible to send a selection of brains around to get an idea of the between scanner effects.

The post hoc harmonisation process has been named as the “travelling brain” substudy of the Lifebrain project.

Collaboration among partners

UiO has proposed a concept for the post hoc harmonisation process based on the concept described in the Lifebrain proposal, at the beginning of April, 2017. There were many pros and cons to sending brains across Europe. External experts have been also invited to contribute to the development of the concept and considering alternative solutions, including the

developers of the FreeSurfer software[1]: Bruce Fischl, Doug Greve and Martin Reuter. The data contributing sites have also sent their comments and questions on the concept, based on which it was revised and operationalized.

After the concept has been approved (see under point 2.1), by the sites, an action plan was created in May, 2017 and a coordination team has been set up to coordinate the logistics of T3.2., with representatives from each contributing site:

- Cristina Solé Padullés (UB)
- Sandra Düzel (MPIB)
- Mikael Stiernstedt (Umeå)
- Tina Emery (UCAM)
- Athanasia Monika Mowinckel (UiO)
- Laura Nawijn (VUmc)
- Louise Baruël Johanssen (REGIONH)
- Work of the team was assisted by the administrative coordinator of Lifebrain, Barbara B. Friedman (UiO)

1. Logistics of the travelling brain tour

1.1. Scanning machines

The scanning machines are the ones used by the Lifebrain cohorts contributing to the Lifebrain database (See Table 1.)

Sites	Name of scanners
Oslo	1.5T Avanto, 3T Skyra, 3T Prisma
Cambridge	3T Prisma
Barcelona	3T Trio
Umeå	3T GE
NESDA	3 identical 3T Philips scanners in Amsterdam, Leiden and Groningen
Copenhagen	3T Philips
MPIB	3T Trio

Table 1. Scanning sites

[1] An open source software suited for processing and analyzing (human) brain MRI images

1.2. Volunteers

All sites have agreed to contribute with 1-2 volunteers each. Altogether 7 volunteers took part in the substudy. One travelling brain has been selected from each of the sites in June, 2017, except for the study site in Amsterdam, where no volunteer was selected and for the study site in Berlin, where both a young and an old travelling brain were selected.

1.3. Costs

Traveling costs and compensation to the volunteers have been covered by the Lifebrain budget of each contributing sites, while scanning costs were covered by the LB budget of each scanning site.

1.4. Scanning dates

The scans were acquired between the 10th July and 27th September, 2017.

1.5. Scanning sequences

The sequences were the same as those used to gather data that will go into the Lifebrain database. The focus has been put on T1-weighted scans, but DTI and rsBOLD were also included if these data were originally collected also.

All participants were scanned twice on each scanner, with a short rest in between (10-60 min). The idea was to get all volunteers scanned at the sites in less than one month, but due to some technical problems and the summer holiday scheduling this was not possible for all sites. However, this small prolongation of the scanning period does not entail any scientific problems.

1.6. Data transfer and sharing

Data (both raw and processed) has been and will be transferred to the UiO Services for sensitive data (TSD) system[2]. The TSD system has been developed and running at the University Centre for Information Technology, University of Oslo. The system has been set up to comply with the Norwegian national and European data protection legislations concerning research on sensitive data, as most of the hosted research projects contain health information that is directly or indirectly identifiable. Authorized users can access the system from any location with internet access using a modern web browser.

Data will be shared by all interested partners in the consortium and outside of the consortium, interested in working on methods for handling scanning variability in collaboration with the Lifebrain consortium. UiO collaborators are Bruce Fischl, Doug Greve, Anastasia Yendiki and Martin Reuter (Harvard University) and Anders M. Dale (University of California San Diego).

[2] https://www.uio.no/english/services/it/research/sensitive-data/about/whitepaper_jan-2017.pdf

Other partners in the consortium may have other collaborators that can contribute in a later phase of the project.

1.7. Ethics approval

UiO has got this substudy approved by the ethical committee in Norway as part of our general Lifebrain approval (See Annex 1. For the original Norwegian and the English version) 16th June, 2017.

2. Concept of the "travelling brains" substudy

2.1. The rationale for the substudy

The main premise behind the substudy was that if we assume that the brain does not change as a function of which scanner it is in, we can try to use this information during pre-processing to "convert" a scan from scanner A into a scan from scanner B. All intra-individual differences in the images are then assumed to be the result of the different scanners.

The idea was that based on data from 7 participants across all the 11 Lifebrain scanners, with two measurements at each site, we could try to generate atlas-based intensity transformations and B1-bias fields which then could be used to correct for scanner differences.

If we scan only once, we may confuse between-scanner variability with within-scanner variability. With two measurements per person/scanner, we can estimate the ratio of within- and between-scanner differences.

2.2. Cons and pros to the concept of the substudy

The pros and cons of the substudy concept have been discussed both in the consortium and outside of the consortium. Alternative solutions were also considered such as correcting for only on the derived measurements or including scanner and protocol as a random effect in the LB analyses.

We summarise the main cons and pros to the substudy below.

2.2.1. Cons

- 7 volunteers will not provide conclusive data to harmonize scans.
- It is uncertain whether this will improve the LB analyses beyond what can be obtained by simply modelling the effect of the site statistically.
- Tweaking/synthesising images may introduce all kinds of differences and the researchers will only be able to check some effects (e.g. the volume or thickness as reported by FreeSurfer). It is difficult to know what effect the procedure has on other

regions of the image or other structures that one does not test (or on specific groups of people/anatomy not seen before, but that is always a problem).

2.2.2. Pros

- It will be very useful in cases with smaller samples sizes where statistical modelling becomes challenging.
- There are many initiatives of sharing MRI data across sites. The output of the tour can be a methodological paper comparing different strategies and assessing how different approaches perform.
- It can be useful in longitudinal studies changing scanners during the course of the study.

The existing database of 250 double-scanned and 20 triple-scanned brains from UiO yields a good opportunity to test different approaches to handle scanner variability, and these can then be applied to the smaller set of travelling brains.

3. Conclusion

The data material for the posterior harmonisation of MRI data has been collected.

7 volunteers have been scanned at 7 contributing Lifebrain sites, altogether at 11 scanning machines. We thus performed in total 154 scan sessions in a relative short period of time (2 months).

We have now started organizing and distributing the data to all interested parties, and are in the process of developing and testing tools for post-hoc scanner corrections. These tools will be used along with the implementation of the analytical tasks under WP4.

ANNEX

Annex 1 Ethics approval for the travelling brain substudy (original in Norwegian in zipped file, translation in English in Annex 1)

Annex 2 Some pictures from the travelling brain tour

Annex 1 Translation of the ethics approval (from Norwegian to English)

To: Anders Martin Fjell

Department of Psychology, University of Oslo

Subject: 2010/3407 Biological predictors for memory – A follow-up study

From: Region: REK Southest (Regional Ethics Committee)

Administrator of case: Mariann Glenna Davidsen, Telephone: +47 22845526 Address: Gullhaugveien 1-3, 0484 Oslo, Norway, E-mail: post@helseforskning.etikkom.no, Web: http://helseforskning.etikkom.no/

Case reference number: 2010/3407/REK south-east B

Date of answer letter: 16.07.2017

Date of application letter: 07.06.2017

Responsible research organisation: Department of Psychology, University of Oslo

Project leader: Anders Martin Fjell

We are writing to you concerning your application regarding changes in the above mentioned research project.

Your case has been handled by the Regional Ethics Committee South-East, based on the Norwegian Health Research Law § 11.

The changes described in the application (*in cursive*):

A small number of healthy adult participants who sign an informed consent will undergo an MRI scanning on their brain at various scanning machines:

- *Oslo University Hospital, Rikshospitalet: 1.5T og 3T (three scanners)*
- *Cambridge University: 3T*
- *Barcelona/University Hospital: 3T*
- *Umeå/Functional Brain Imaging Center: 3T*
- *Amsterdam/ Leiden: 3T (to scanners)*
- *Copenhagen/Hvidover Hospital: 3T Berlin*
- *Berlin/Max Plank Institute: 3T*

The sequences to be applied:

- *T1-weighted*
- *T2-weighted*
- *Diffusion Tensor Imaging (DTI)*
- *Multi-echo MPRAGE*

Total scanning time for each scanning will be lower then 60 minutes (might vary by scanner).

These participants will be recruited specifically for this study and will not take part in the usual medical check-up of the original study. Information on age, sex and handedness will be used in an unidentifiable form.

The evaluation of the committee:

The committee has no objections to the planned changes in the research.

The participation requires informed consents, and only participants who can give their consents, are healthy persons and are over 18 years that can participate. The travel costs (etc.) of the participants will be covered by the project.

Measure

The committee has evaluated the changes and accepts it based on the Norwegian Health Research Law § 11.

The acknowledgement is provided with the condition that the study is implemented as to the changes reported in the application.

In case of complaints, the National Research Committee for Medicine and Health is the relevant organization, based on the Norwegian Public Administration Law§ 28. The complaints should be sent to the REK South-East. The deadline for filing complaints is three weeks upon receiving this letter.

We ask you to send your questions and request via our case managing portal: http://helseforskning.etikkom.no or through e-mail: post@helseforskning.etikkom.no.

Please provide your reference number in the correspondence.

Your sincerely,

Grete Dyb

professor, dr. med.

Head of REK South-East

Mariann Glenna Davidsen consultant

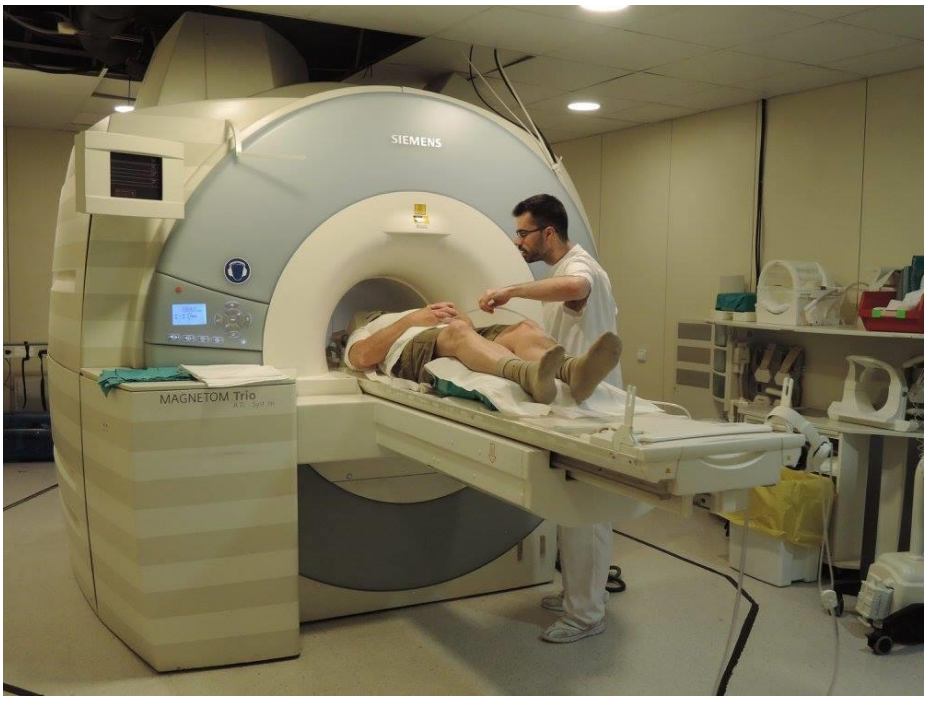
Copy to:

University of Oslo Central Administration

Head of institute, Siri Gullestad, Department of Psychology, University of Oslo

Annex 2 Photos from the travelling brain tour

Barcelona

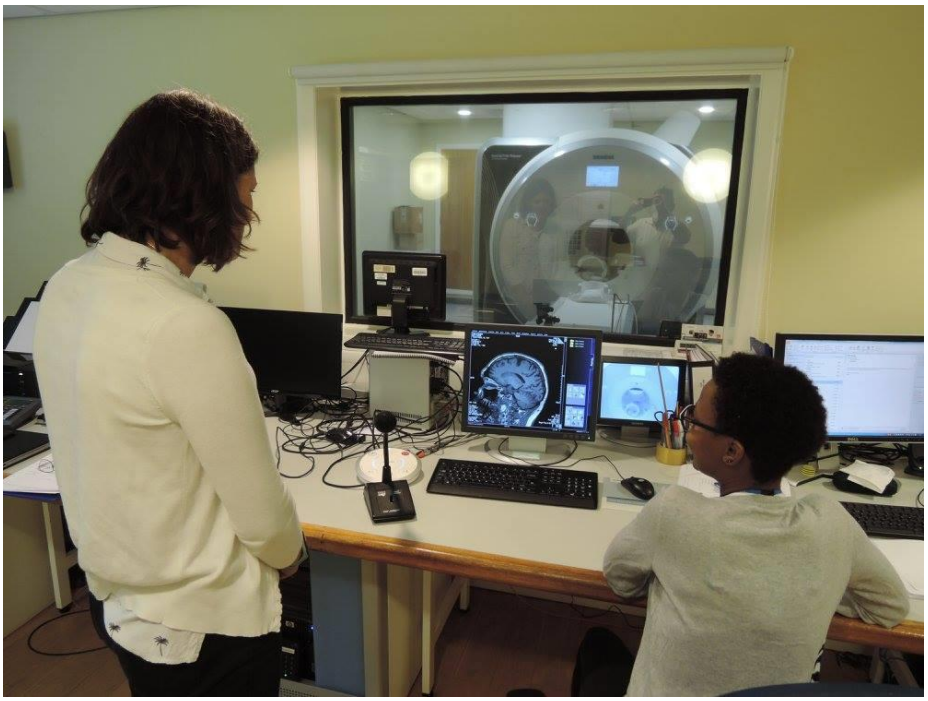


3 T scanner in Barcelona

Control room in the University Hospital, Barcelona

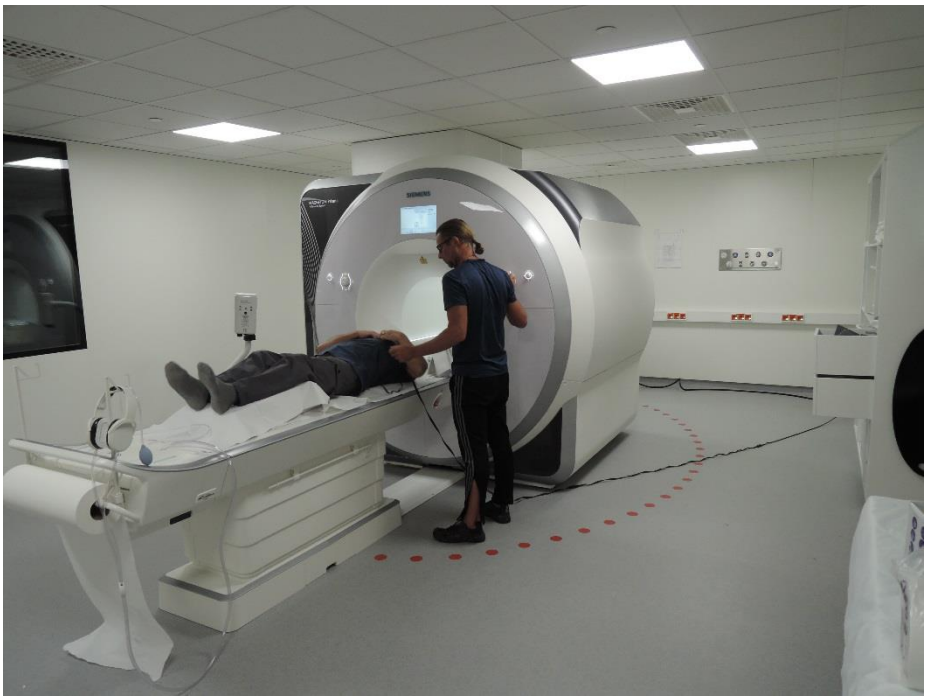
Cambridge

Prisma scanner in Cambridge



Control room in the MRI Centre, Cambridge

Oslo

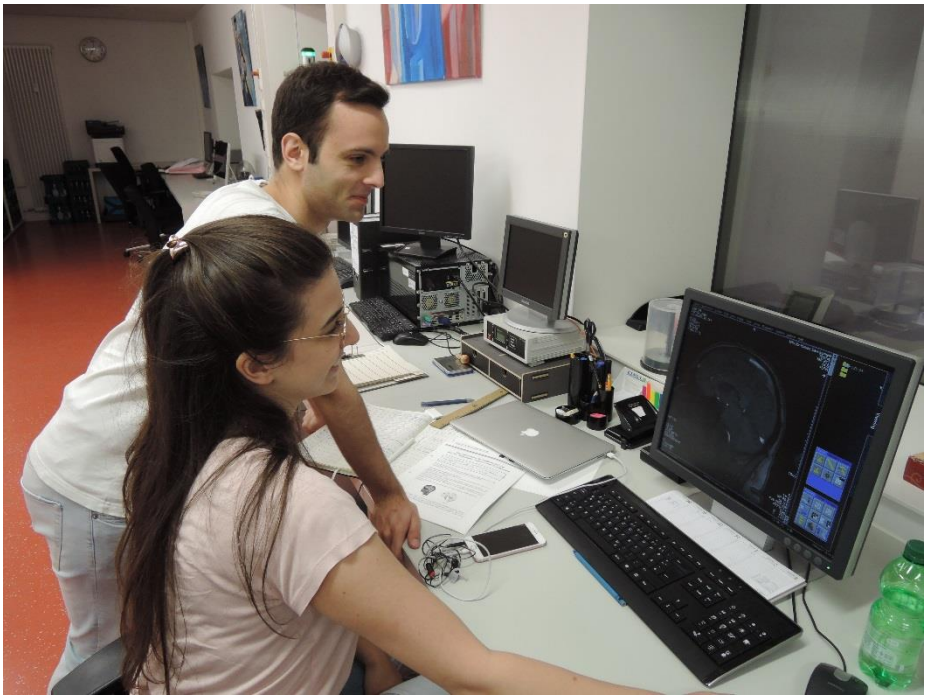


Rikshospitalet, Oslo

Control room in Rikshospitalet, Oslo

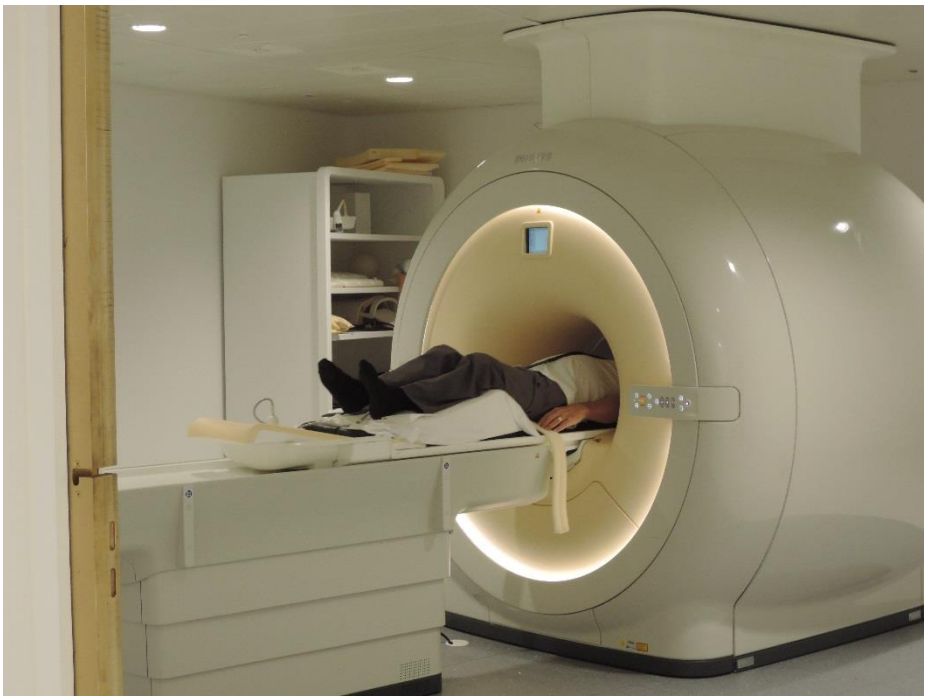
Berlin

3 T Trio scanner in Berlin



Control room in the MRI Center in Berlin

Amsterdam



3 T Philips scanner

Control room in the Spinoza MRI Center in Amsterdam

Copenhagen

Hvidovre Hospital, Copenhagen