# Using the UK Biobank Imaging data

**1st Australian UK Biobank Research Symposium Brisbane, Australia 2024** 

**Baptiste Couvy-Duchesne** 

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## **Overview of today's session**

#### Introduction – and overview of the UKB imaging data

Baptiste Couvy-Duchesne

#### Focus on structural brain MRI (T1w)

Elise Delzant

#### Connectomes from brain data (structural and functional) Caio Seguin

## What does your imaging assessment visit involve?

The imaging assessment lasts around 4-5 hours and involves taking imaging scans of your internal organs and the collection of more information about your health and lifestyle, along with a small donation of blood.

https://www.ukbiobank.ac.uk/explore-yourparticipation/imaging-study-updates

Repeat imaging – aiming for >60,000 individuals reimaged



#### Summary of the Imaging visits

MRI Brain Heart Abdominal/body

#### Utrasound carodid

Dual energy X ray (DXA) whole body

Electrocardiogr am (ECG) Heart





Retinal optical coherence tomography \*







\* Brought back in repeat imaging session

#### Data types

Imaging derived phenotypes - IDPs

Bulk files

22677	Mean carotid IMT (intima-medial thickness) at 210 degrees	
22680	Mean carotid IMT (intima-medial thickness) at 240 degrees	
22670	Minimum carotid IMT (intima-medial thickness) at 120 degrees	
22673	Minimum carotid IMT (intima-medial thickness) at 150 degrees	
22676	Minimum carotid IMT (intima-medial thickness) at 210 degrees	
22679	Minimum carotid IMT (intima-medial thickness) at 240 degrees	
22682	Quality control indicator for IMT at 120 degrees	
22683	Quality control indicator for IMT at 150 degrees	
22684	Quality control indicator for IMT at 210 degrees	
22685	Quality control indicator for IMT at 240 degrees	
20222	Carotid artery ultrasound image (left)	1
20223	Carotid artery ultrasound image (right)	1
20226	Carotid artery ultrasound report	1
20241	Raw carotid device data	1

• 4 fields marked ‡ are blob/bulk.

# Eye imaging

#### Eye measures – <u>Refractometer</u>



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## biobank\*

Category 100014 Assessment centre 

Eye measures 

Refractometry 

Refractometry 1

#### Description

This category contains data on measurements related to the assessment of the participant's eye prescription (refractive error), using a TomeyRC - 5000 device. This category includes data on whether the measurement was made, and the test result for refractometry (Sphere, Cylinder, Axis, Pupil diameter) and keratometry (corneal refraction and astigmatism) for each eye. This measure was added to the assessment visit towards the end of recruitment and continued through the repeat visit in 2012.

Browse



Index

#### Eye measures - <u>Retinal optical coherence tomography</u>

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#### *biobank*\*

Category 100016 Assessment centre > Eye measures > Retinal optical coherence tomography

#### Description

This category contains data on optical imaging (Coherence Tomography) of the retina. The instrument takes a 3D scan and photograph of the retina and also provides a magnified photograph of the fundus. This category includes data on whether the measurement was performed, and imaging data of each eye.

Index

This measure was added to the assessment visit towards the end of recruitment and also carried out during the initial re-assessment phase in 2012 using the TOPCON 3D OCT 1000 Mk2. It was not part of the standard imaging protocol but was re-introduced at the end of 2022 for participants being re-imaged using the TOPCON Triton device.

#### Article | Open access | Published: 03 November 2022

UK Biobank retinal imaging grading: methodology, baseline characteristics and findings for common ocular diseases

Alasdair N. Warwick, Katie Curran, Barbra Hamill, Kelsey Stuart, Anthony P. Khawaja, Paul J. Foster, Andrew J. Lotery, Michael Quinn, Savita Madhusudhan, Konstantinos Balaskas, Tunde Peto <sup>⊠</sup> & UKBB Eye and Vision Consortium

Eye 37, 2109–2116 (2023) Cite this article

#### Age-related macular degeneration (AMD) Glaucoma Retinopathy.

# Heart imaging

#### **Heart measurements**

ibiobank <sup>**</sup>	Index	Browse	Search	Catalogues	Downloads	Login	Help
Category 104 Assessment centre ► Physical measures ► ECG at rest, 12-lead							
Description							
12-lead ECG							



#### ibiobank\*

Category 102 Assessment centre ► Imaging ► Heart MRI

Description Chest MRI imaging



Figure 3: Aortic valve flow imaging view planned using the sagittal and coronal left ventricular outflow tract (LVOT) cines

https://biobank.ndph.ox.ac.uk/ukb/ukb/docs/cardiac\_mri\_explan.pdf

## Heart (Chest) MRI

> Eur Heart J Cardiovasc Imaging. 2021 Feb 22;22(3):251-258. doi: 10.1093/ehjci/jeaa297.

#### Cardiovascular magnetic resonance imaging in the UK Biobank: a major international health research resource

Zahra Raisi-Estabragh <sup>1 2</sup>, Nicholas C Harvey <sup>3 4</sup>, Stefan Neubauer <sup>5</sup>, Steffen E Petersen <sup>1 2</sup>

Affiliations + expand PMID: 33164079 PMCID: PMC7899275 DOI: 10.1093/ehjci/jeaa297 Free PMC article

"The cardiovascular magnetic resonance (CMR) scan provides detailed assessment of cardiac structure and function comprising bright blood anatomic assessment (sagittal, coronal, and axial), left and right ventricular cine images (long and short axes), myocardial tagging, native T1 mapping, aortic flow, and imaging of the thoracic aorta"



A gif of one chest MRI



# UK Biobank: opportunities for cardiovascular research a

Thomas J Littlejohns 🖾, Cathie Sudlow, Naomi E Allen, Rory Collins

*European Heart Journal*, Volume 40, Issue 14, 07 April 2019, Pages 1158–1166, https:// doi.org/10.1093/eurheartj/ehx254

Published: 20 May 2017 Article history -

"Classification and sub-classification of diseases can be enhanced through combining the diverse phenotypic and genotypic data with medical records. The large sample size enables researchers to perform risk stratification on well-defined phenotypes to focus on high- and low-risk populations for cardiovascular disease, e.g. those with the lowest and highest levels of circulating lipid levels. Additionally, mechanistic pathways between risk factors and outcomes can be explored using the genetic, biomarker and imaging data."

#### **Real-life heart monitoring**

If you are 65 years or older at the time of your visit, we may also ask if you would be prepared to wear a heart monitoring patch for 14 days. This is a water-resistant adhesive patch that is applied to your skin over the heart and which will provide information on heart rhythm. We will give this to you when you visit us, together with a box so that you can return the device to us after the 14-day period. *Irhythm* or *Preventice* device –

Data restricted



#### From INFORMATION LEAFLET for participants

# *biobank*\*

Category 347 Additional exposures ► Cardiac monitoring

Description Cardiac monitoring

# Body composition DXA scan

#### **Bones and body composition - DXA**

#### DXA (dual-energy X-ray absorptiometry) scan

- The DXA scan takes about 20 minutes.
- We will ask you to lie on a firm table while an arm of the scanner passes over you (see picture) to take X-ray images of your bones. We will ask you to lie in various positions so that the scanner can take images of different parts of your body.

From INFORMATION LEAFLET for participants



https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/DXA\_explan\_doc.pdf

## Bones and body composition - DXA

Bone size, mineral content and density Osteoarthritis

Bone mass

Fat mass

Lean mass

Fat percentage

Category 103 Assessment centre ► Imaging ► DXA assessment

Description

Whole body DXA imaging.

2 Sub-Categories		5 Data-Fields	1 Parent Ca	tegory
Category ID	) Descrij	otion		Items
125	Bone si	Bone size, mineral and density by DXA		
124	Body co	omposition by DX	A	72

https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/DXA\_explan\_doc.pdf







# Abdominal MRI



## Abdominal (Body) MRI scan

## ibiobank"

Category 105 Assessment centre ► Imaging ► Abdominal MRI

#### Description

Abdominal MRI scans

5 Sub-Categories		4 Data-Fields	1 Parent Ca	
Category ID Description			tems	
156	Kidney MRI			4+5
126	Liver MRI			7
131	Pancreas MRI			4
149	Abdominal composition			28
158	Abdominal organ composition			<mark>19</mark>





An axial image showing the liver at its maximum size on axial image



An axial fat sat image showing the pancreas

https://biobank.ctsu.ox.ac.uk/crystal/ukb/docs/body\_mri\_explan.pdf

#### **Kidney**

> Sci Rep. 2020 Dec 1;10(1):20963. doi: 10.1038/s41598-020-77981-4.

#### Kidney segmentation in neck-to-knee body MRI of 40,000 UK Biobank participants

Taro Langner <sup>1</sup>, Andreas Östling <sup>2</sup>, Lukas Maldonis <sup>3</sup>, Albin Karlsson <sup>2</sup>, Daniel Olmo <sup>2</sup>, Dag Lindgren <sup>3</sup>, Andreas Wallin <sup>3</sup>, Lowe Lundin <sup>3</sup>, Robin Strand <sup>2 4</sup>, Håkan Ahlström <sup>2 3</sup>, Joel Kullberg <sup>2 3</sup>

Affiliations + expand PMID: 33262432 PMCID: PMC7708493 DOI: 10.1038/s41598-020-77981-4 Free PMC article

Uppsala University, Sweden

-Fields	1 Parent Category			
Field ID Description				
Kidney	distance			
Kidney	fusion			
Kidney	parenchyma (left)			
Kidney	parenchyma (right)			
Kidney	parenchyma total			
	Fields Descrip Kidney Kidney Kidney Kidney			



#### Liver

> PLoS One. 2017 Feb 27;12(2):e0172921. doi: 10.1371/journal.pone.0172921. eCollection 2017.

#### Characterisation of liver fat in the UK Biobank cohort

Henry R Wilman <sup>1 2</sup>, Matt Kelly <sup>1</sup>, Steve Garratt <sup>3</sup>, Paul M Matthews <sup>4</sup>, Matteo Milanesi <sup>1</sup>, Amy Herlihy <sup>1</sup>, Micheal Gyngell <sup>1</sup>, Stefan Neubauer <sup>1 5</sup>, Jimmy D Bell <sup>2</sup>, Rajarshi Banerjee <sup>1</sup>, E Louise Thomas <sup>2</sup>

Affiliations + expand PMID: 28241076 PMCID: PMC5328634 DOI: 10.1371/journal.pone.0172921 Free PMC article

Reference range of liver corrected T1 values in a population at low risk for fatty liver disease-a UK Biobank sub-study, with an appendix of interesting cases

A Mojtahed <sup>1</sup>, C J Kelly <sup>2</sup>, A H Herlihy <sup>2</sup>, S Kin <sup>2</sup>, H R Wilman <sup>2</sup> <sup>3</sup>, A McKay <sup>2</sup>, M Kelly <sup>2</sup>, M Milanesi <sup>2</sup>, S Neubauer <sup>2</sup> <sup>4</sup>, E L Thomas <sup>3</sup>, J D Bell <sup>3</sup>, R Banerjee <sup>2</sup>, M Harisinghani <sup>5</sup> Affiliations + expand PMID: 30032383 PMCID: PMC6348264 DOI: 10.1007/s00261-018-1701-2 Free PMC article

# 7 Data-Fields1 Parent CategoryField ID Description20204Liver Imaging - T1 ShMoLLI - DICOM ‡20254Liver imaging - IDEAL protocol - DICOM ‡20203Liver imaging - gradient echo - DICOM ‡40061Proton density fat fraction (PDFF)40062Liver iron corrected T1 (ct1)

- 40060 Liver iron (Fe)
- 40063 Acquisition protocol

#### • 3 fields marked ‡ are blob/bulk.



#### AMRA<sup>®</sup> Medical AB (Linköping, Sweden)

https://biobank.ctsu.ox.ac.uk/crystal/ukb /docs/AMRA\_derived\_explan\_doc.pdf https://biobank.ctsu.ox.ac.uk/crystal/lab el.cgi?id=149

Calico (Calico Life Sciences LLC, South San Francisco, USA) and the University of Westminster

https://biobank.ctsu.ox.ac.uk/crystal/lab el.cgi?id=158

Volume, fat, and iron in organs and tissues



> Elife. 2021 Jun 15:10:e65554. doi: 10.7554/eLife.65554.

#### Genetic architecture of 11 organ traits derived from abdominal MRI using deep learning

Yi Liu <sup>1</sup>, Nicolas Basty <sup>2</sup>, Brandon Whitcher <sup>2</sup>, Jimmy D Bell <sup>2</sup>, Elena P Sorokin <sup>1</sup>, Nick van Bruggen <sup>1</sup>, E Louise Thomas <sup># 2</sup>, Madeleine Cule <sup># 1</sup>

Affiliations + expand PMID: 34128465 PMCID: PMC8205492 DOI: 10.7554/eLife.65554 Free PMC article

# Carotid ultrasound

#### **Carotid ultrasound**

Left and right measurements Manual + automated measurements Quality control **Artery intima-media thickness (cIMT)** is a marker of subclinical **atherosclerosis (**buildup of cholesterol plaque in the walls of arteries)

https://biobank.ndph.ox.ac.uk/ukb/ukb/docs/ carult\_explan\_doc.pdf



Arterioscler Thromb Vasc Biol. 2022 Apr; 42(4): 484–501. Published online 2021 Dec 2. doi: 10.1161/ATVBAHA.121.317007 PMCID: PMC8939707 PMID: <u>34852643</u>

Twenty-Five Novel Loci for Carotid Intima-Media Thickness: A Genome-Wide Association Study in >45 000 Individuals and Meta-Analysis of >100 000 Individuals

<u>Ming Wai Yeung</u>,<sup>1</sup> <u>Siqi Wang</u>,<sup>3,1,2</sup> <u>Yordi J. van de Vegte</u>,<sup>1</sup> <u>Oleg Borisov</u>,<sup>4</sup> <u>Jessica van Setten</u>,<sup>2</sup> <u>Harold Snieder</u>,<sup>2</sup> <u>Niek Verweij</u>,<sup>1</sup> <u>M. Abdullah Said</u>,<sup>1</sup> and <u>Pim van der Harst</u><sup>⊠1,3</sup>

▶ Author information ▶ Article notes ▶ Copyright and License information PMC Disclaimer

# Brain MRI

#### **Brain MRI**

Notes	9 Sub-Categories	5 Data-Fields	1 Parent	Category	
Catego	Items				
108	2				
110	T1 structural brain MRI				
112	T2-weighted brai	T2-weighted brain MRI			
119	Arterial spin labe	Arterial spin labelling brain MRI			
106	Task functional b	rain MRI		34	
107	Diffusion brain M	IRI		14+684	
111	Resting function	al brain MRI		48+6	
109	Susceptibility we	ighted brain MRI		38	
200	Native atlases			1+13	



Bulk files – raw and processed images >3,000 IDPs (Imaging Derived Phenotypes)

#### **Brain MRI – must read**

Resource Published: 19 September 2016

#### Multimodal population brain imaging in the UK Biobank prospective epidemiological study

Karla L Miller <sup>I</sup>, Fidel Alfaro-Almagro, Neal K Bangerter, David L Thomas, Essa Yacoub, Junqian Xu, Andreas J Bartsch, Saad Jbabdi, Stamatios N Sotiropoulos, Jesper L R Andersson, Ludovica Griffanti, Gwenaëlle Douaud, Thomas W Okell, Peter Weale, Iulius Dragonu, Steve Garratt, Sarah Hudson, Rory Collins, Mark Jenkinson, Paul M Matthews & Stephen M Smith

Nature Neuroscience 19, 1523–1536 (2016) Cite this article

32k Accesses 804 Citations 283 Altmetric Metrics

# **Brain Imaging Documentation**

https://biobank.ndph.ox.ac.uk/ukb/ukb/docs/brain\_mri.pdf

#### **Brain MRI – defacing & processing**



> Neuroimage. 2018 Feb 1:166:400-424. doi: 10.1016/j.neuroimage.2017.10.034. Epub 2017 Oct 24.

#### Image processing and Quality Control for the first 10,000 brain imaging datasets from UK Biobank

Fidel Alfaro-Almagro <sup>1</sup>, Mark Jenkinson <sup>2</sup>, Neal K Bangerter <sup>3</sup>, Jesper L R Andersson <sup>2</sup>, Ludovica Griffanti <sup>2</sup>, Gwenaëlle Douaud <sup>2</sup>, Stamatios N Sotiropoulos <sup>4</sup>, Saad Jbabdi <sup>2</sup>, Moises Hernandez-Fernandez <sup>2</sup>, Emmanuel Vallee <sup>2</sup>, Diego Vidaurre <sup>5</sup>, Matthew Webster <sup>2</sup>, Paul McCarthy <sup>2</sup>, Christopher Rorden <sup>6</sup>, Alessandro Daducci <sup>7</sup>, Daniel C Alexander <sup>8</sup>, Hui Zhang <sup>8</sup>, Iulius Dragonu <sup>9</sup>, Paul M Matthews <sup>10</sup>, Karla L Miller <sup>2</sup>, Stephen M Smith <sup>2</sup> Non-defaced MRI accessible upon request – restricted field

#### Structural Brain MRI – T1w, T2-FLAIR, SWI



(g) Manhattan plot (a layout common in genetic studies) relating all 25 IDPs from the T1 data to 1,100 non-brainimaging variables extracted from the UK Biobank database. Effects such as age, sex and head size are regressed out of all data before computing the correlations. Here, the maximum  $r^2 = 0.045$  and the minimum  $r^2 = 0.0058$ . (h) Plot relating all 14 T2\* IDPs 1,100 non-imaging to variables. Maximum  $r^2$  = 0.034, minimum  $r^2 = 0.0063$ . Marked Bonferroni and FDR multiple comparison threshold levels are presented as in g.

Multimodal population brain imaging in the UK Biobank prospective epidemiological study

#### **Diffusion Brain MRI**



(e) Plot relating all 675 dMRI IDPs (nine distinct dMRI modeling outputs from tensor and NODDI models × 75 tract masks) 1,100 non-imaging to variables (see Fig. 1g for details). Maximum  $r^2$  = 0.057, minimum  $r^2$ (passing Bonferroni) = 0.0065. Dotted horizontal lines (multiple comparison thresholds) are described in Figure 1g.

Cognitive

Multimodal population brain imaging in the UK Biobank prospective epidemiological study

#### **Resting-state fMRI**



(c) Plot relating the 76 rfMRI 'node amplitude' IDPs to 1,100 non-imaging variables (see Fig. 1g for details). Maximum  $r^2$  = 0.065, minimum  $r^2$ (passing Bonferroni) = (d) Plot relating 0.0059. rfMRI the 1,695 'functional connectivity' IDPs to 1,100 non-imaging variables. Maximum  $r^2$  = 0.032, minimum  $r^2$  = 0.0059. Dotted horizontal lines (multiple comparison thresholds) in c and d are described in Figure 1g.

Multimodal population brain imaging in the UK Biobank prospective epidemiological study

#### Task fMRI – Emotion processing







#### Hariri faces/shapes "emotion" task

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.

Emotion processing Visual regions Face recognition

#### Task fMRI – Emotion processing



(e) Plot relating the 16 tfMRI IDPs to 1,100 non-imaging variables (see Fig. 1g for details). Maximum  $r^2 = 0.018$ , minimum  $r^2$  (passing Bonferroni) = 0.0062. Dotted horizontal lines (multiple comparison thresholds) are described in Figure 1g.

#### **GWAS of brain IDPs**

Article Open access Published: 10 October 2018

## Genome-wide association studies of brain imaging phenotypes in UK Biobank

Lloyd T. Elliott, Kevin Sharp, Fidel Alfaro-Almagro, Sinan Shi, Karla L. Miller, Gwenaëlle Douaud, Jonathan Marchini <sup>I</sup> & Stephen M. Smith <sup>I</sup>

Nature 562, 210–216 (2018) Cite this article

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2018 3,144 brain IDPs N=8,428 participants

Nat Neurosci. Author manuscript; available in PMC 2021 May 9.	PMCID: PMC7610742
Published in final edited form as:	EMSID: EMS123172
<u>Nat Neurosci. 2021 May 1; 24(5): 737–745.</u>	PMID: <u>33875891</u>

Published online 2021 Apr 19. doi: 10.1038/s41593-021-00826-4

An expanded set of genome-wide association studies of brain imaging phenotypes in UK Biobank

Stephen M Smith,<sup>1</sup> Gwenaëlle Douaud,<sup>1</sup> Winfield Chen,<sup>2</sup> Taylor Hanayik,<sup>1</sup> Fidel Alfaro-Almagro,<sup>1</sup> Kevin Sharp,<sup>3</sup> and Lloyd T Elliott<sup>2,\*</sup>

2021 3,935 brain IDPs N=39,691 participants

# Tips about getting started with UK Biobank images



#### Some tips



Check overlap between trait/disease of interest and imaging sessions





Explore data returned by other research groups

Are available IDPs enough for the analysis ?





If bulk – need resources – e.g. High Performance Cluster, RAP



Imaging expert for processing / analyses



Keep in mind returning data to UK Biobank

# From IDPs to vertex/voxel wise analyses

## Starting point





- High dimensional
  - 10M common SNPs
  - 1M cortical structure measurements)
- **Complex pattern of correlation** (LD / connectome)



```
\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{u} + \mathbf{e}\mathbf{u} \sim \mathcal{N}(0, \mathbf{I}\sigma_{\mathbf{b}}^{2}/p)
```

Morphometricity

$$m^{2} = \frac{\widehat{\sigma_{\rm b}^{2}}}{(\widehat{\sigma_{\rm b}^{2}} + \widehat{\sigma_{\rm e}^{2}})}$$

- Total association with vertex-wise data
- Information contained in brain image



#### Morphometricity

N=8,662 UKB participants M~650,000 brain measurements 168 phenotypes tested

• 58 with significant morphometricity

<u>A unified framework for association and prediction from vertexwise grey-matter structure</u>, Couvy-Duchesne et al., <u>Human Brain</u> <u>Mapping</u>, 2020

Applications to compare MRI processing Furtjes et al., <u>Cortex</u>, 2023 Delzant et al., in preparation



 $\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{u} + \mathbf{e}$  $\mathbf{u} \sim \mathcal{N}(0, \mathbf{I}\sigma_{\mathbf{b}}^2/\mathbf{p})$ 





 $\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{u} + \mathbf{e}$  $\mathbf{u} \sim \mathcal{N}(0, \mathbf{I}\sigma_{\mathbf{b}}^{2}/p)$ 



## **Brain-mapping models**

 $\mathbf{Y} = \mathbf{X}_{i}b_{i} + \mathbf{Z}\mathbf{C} + \boldsymbol{\varepsilon} \qquad \text{GLM}$ 

 $\mathbf{Y} = \mathbf{X}_{i}\mathbf{b}_{i} + \mathbf{Z}\mathbf{c} + \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}$  Imm

X : Nxp matrix of all standardised vertex-wise measurements,

*Z* : Nxq of q covariates

*c* : the q fixed effects

 $\beta$ : vector of joint vertex-trait associations, random effects, allowing for p>N, with  $\beta \sim \mathcal{N}(0, I\sigma_{\beta}^2)$ 

 $\boldsymbol{\epsilon}$  : error term assumed to follow  $\boldsymbol{\epsilon} \sim \mathcal{N}(0, \mathbf{I}\sigma_{\boldsymbol{\epsilon}}^2)$ .

 $\sigma_{\beta}^2$  and  $\sigma_{\epsilon}^2$ : the variances of the random effects  $\beta$  and  $\epsilon$ .



## Thank youTo all participants and data collection teams – UKB application 12505



Algorithmes, modèles et méthodes pour les images et les signaux du cerveau humain (ARAMIS) Paris Brain Institute



**Program for Complex Trait Genomics (PCTG)** Institute for Molecular Bioscience, the University of Queensland



Github/baptisteCD/brainMapR (R-package for brain plots and gifs) Couvy-Duchesne et al., <u>Human Brain Mapping</u>, 2020 Couvy-Duchesne et al., <u>IEEE 17th ISBI</u>, 2020 Couvy-Duchesne et al., <u>SPIE Medical Imaging</u>, 2021 Couvy-Duchesne et al., <u>JMI</u>, 2022 Furtjes et al., <u>Cortex</u>, 2023