EBRAINS 2.0

D2.4 - Strategy for 5M connector data acquisition

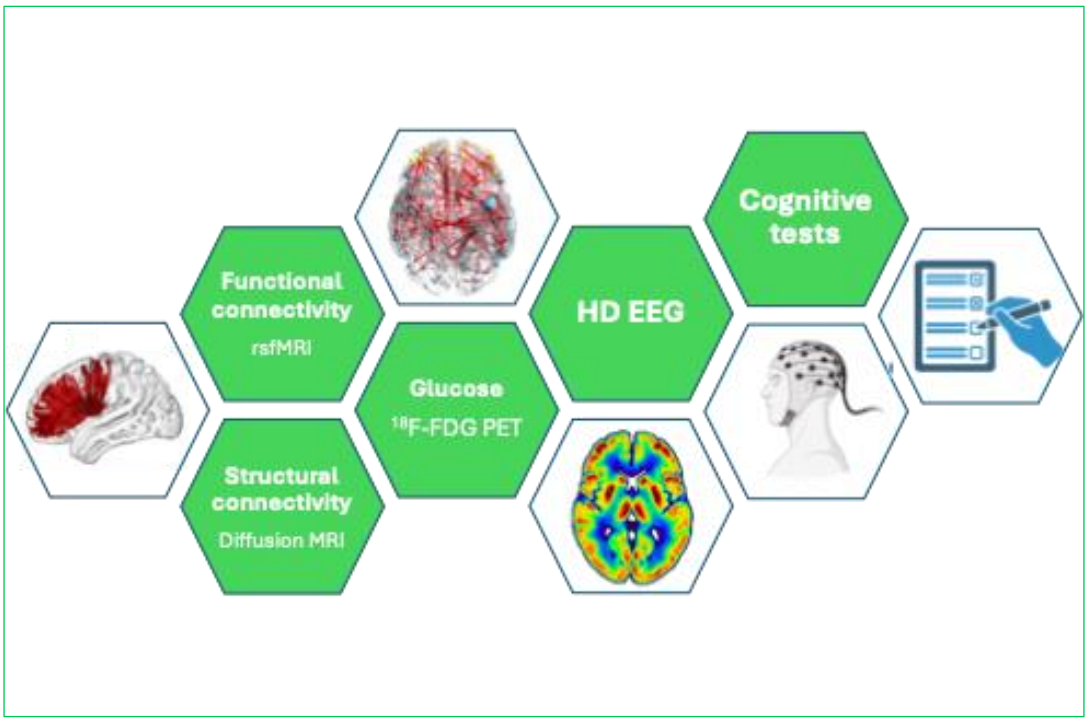

Figure 1: The 5M dataset

Funded by the European Union

EBRAINS 2.0 has received funding from the European Union's Research and Innovation Program Horizon Europe under Grant Agreement No. 101147319.

Funded by the European Union

Project Number:	101147319	Project Name:	EBRAINS 2.0

Deliverable No. & Name:	D2.4 Strategy for 5M connectome data acquisition
Deliverable Description:	Report on the strategy to follow during the multi-site acquisition of the 5M connectome dataset
Deliverable Type:	R – Document report
Dissemination Level:	PU – Public
Planned Delivery Date:	Project Month 4 / 30 April 2024
Actual Delivery Date:	Project Month 4 / 30 April 2024
Author(s):	Alessandra BERTOLDO, UNIPD (P7)
Compiled by:	Alessandra BERTOLDO, UNIPD (P7)
Contributor(s):	Gitte Moos KNUDSEN, REGIONH (P21), Section contributed: 1.1/1.6 Valentin RIEDL, TUM-MED (P48), Section contributed: 1.1/1.6 Rupert LANZENBERGER, MUW (P44), Section contributed: 1.1/ 1.6 Andreas HAHN, MUW (P44), Section contributed: 1.1/ 1.6 Katarzyna KURCYUS, TUM-MED (P48), Section contributed: 1.1/ 1.6
WP QC Review:	Andreea Stefania RADU, UNIPD (P7)
WP Leadership Sign-off:	Maurizio CORBETTA, UNIPD (P7)
Project QC Review:	Marie COUËDIC, EBRAINS-AISBL (P1)
Funding:	EBRAINS 2.0 has received funding from the European Union's Research and Innovation Program Horizon Europe under Grant Agreement No. 101147319.
Keywords:	Brain research, digital research infrastructure, atlases, 5M connectome, FAIR data
Abstract:	This deliverable outlines the experimental strategy for acquiring the data which will be utilized to encode the 5M Connectome in WP2. The data needed to describe the complex multimodal organization of the brain network will be obtained using a hybrid scanner in conjunction with EEG signal acquisition. For each individual, multiple modalities including structural and functional MRI, metabolism from PET, and electrophysiology from EEG will be measured simultaneously, both within individual subjects and across multiple subjects, in order to address the issue of intersubject variability. To further evaluate the reliability of the EEG/MR protocol across different sites, a 'travelling heads' approach will be employed, wherein healthy volunteers will be scanned once at each site. Additionally, a battery of cognitive tests will be administered to provide further characterization of the individuals.

Table of Contents

Table of Figures

Table of Tables

1. The unified protocol

The task involves the development of a strategy for a multimodality imaging protocol to be used for a multicentre and mono-scanner imaging acquisition in healthy controls. This unique dataset, one which has never been acquired before, will be collected thanks to the collaboration of four leading imaging centres in Europe equipped with the same Siemens Biograph mMRn PET/MRI scanner. The principal aim is to gather unique, comprehensive, multi-scale and multi-modal neuroimaging dataset from healthy participants to be also used to detect abnormalities in pathological brains. Five different imaging modalities are considered: positron emission tomography (PET) with 18F-FDG, T1w MRI, resting state fMRI, diffusion MRI and EEG, all acquired simultaneously. All modality acquired from healthy individuals within the age range of 21-79 years.

1.1 Subjects

The expected total number of individuals is 204 (24 UNIPD + 60 TUM-MED + 60 MUW + 60 REGIONH). More specifically:

Table 1: Age Range

SUBJECTS	
Range 21-40 yrs	• 34F & 34M
Range 41-60 yrs	• 34F & 34M
Range 60-79 yrs	• 34F & 34M

F= female, M= male

Before the multimodal acquisition, preferably on the same day or a maximum of two days before or later, subjects will be tested with the same battery of cognitive tests for neuropsychological assessment across all centres. The battery includes Raven Standard Progressive Matrices, Vocabulary (WAIS-IV), Rey Auditory Verbal Learning Test, Symbol Digit Modalities Test, Verbal Fluency, Nine-Hole Pegboard Test, Motor Screening Task, totalling 30 minutes.

Before the multimodal acquisition, subjects should fast for at least 6 h (fast means also no coffee and alcohol), no smoking. The glucose concentration in blood will be measured before each PET scan. Blood glucose levels will be acceptable if between 70 mg/dl and 100 mg/dl and, however, according to the local laboratory reference. Before the scanning procedure, subjects should void their bladder for maximum comfort. Pregnancy must be excluded in fertile women by urine pregnancy tests before the PET/MR scan. Further exclusion criteria are history of or current substance abuse as well as usage of medication. Subjects are instructed to stay awake with eyes open (fixation cross) while being scanned.

Each centre will aim to acquire 33% of the subjects in each of the three age ranges:

Table 2: Division of the acquisitions among age ranges and centres

SUBJECTS	UNIPD	TUM-MED	MUW	REGIONH
Range 21-40 yrs	• 4M & 4F	• 10M & 10F	• 10M & 10F	• 10M & 10F
Range 41-60 yrs	• 4M & 4F	• 10M & 10F	• 10M & 10F	• 10M & 10F
Range 60-79 yrs	• 4M & 4F	• 10M & 10F	• 10M & 10F	• 10M & 10F

F= female, M= male

Included subjects' codes, their gender, and year of birth, will be shared among the 4 centres to monitor the coverage of the final age range 21-79.

1.2 Scanner

In each of the 4 centres, the same hybrid scanner is available, i.e., Siemens Biograph mMR with head neck coil of 16 channels (4 for neck and 12 for brain). Each scanner will be equipped with the same Multiband sequence:

c2p Minnesota (CMRR MB/SMS EPI Sequences: Release R016a), Software: VE11P-SP04, obtained from the CMRR homepage (https://www.cmrr.umn.edu/multiband/).

Each scanner will be also equipped with the same c2p multi PLD pCASL sequence (from Danny JJ Wangs, UCLA, USA) obtained from Siemens.

1.3 EEG System

EEG signals will be acquired simultaneously with PET and rsfMRI. UNIPD and REGIONH will use the EGI Geodesic 256-channel EEG system with MR-compatible head caps (in 3 sizes). MUW will use the 96 channels BrainCap MR Brain Products with Carbon Wire Loops for motion artefact correction. TUM-MED is planning to use a similar system similar to the one used by MUW.

Noteworthy, the EEG acquisition parameters will be set close to the utmost possible sampling rate for analog-digital conversion. Standardized data pre-processing and processing pipelines will also be implemented.

1.4 PET 18F-FDG acquisitions

Injection: the cannula for i.v. administration should be in place at least 10 min before 18F-FDG administration. At time 0 min a bolus of 2.5 MBq/kg (expected average of 185 MBq) will be injected over 60 seconds.

Blood sampling: radial artery will be used to draw the arterial blood samples to define the arterial input function. Automatic sampling will be performed for the first 3 min at a rate of 4 mL/min. Manual samples will be acquired every 5 minutes from minute 5 until the end of the experiment.

In addition, 4 manual venous blood samples will be obtained (by considering that arteriovenous equilibration is reached after ~15–20 minutes) at 25, 30, 40, 50 min post-injection from the cubital vein simultaneously with the arterial samples and will be processed in the same way. Due to technical limitations, UNIPD will only collect venous samples.

18F-FDG: PET data will be acquired dynamically. Recording of 60 min PET data in list-mode will start simultaneously with the radioligand administration. The image reconstruction pipeline will be the same for all the data and include correction for scatter, dead time, attenuation (due to head and radio-frequency coil), tracer decay and normalization. Reconstruction will be performed with Poisson ordered subset expectation maximization (3 iterations and 21 subsets) no spatial smoothing will be performed after reconstruction.

1.5 MR acquisitions

The following MRI data will be acquired on the 3T Siemens Biograph mMR scanner equipped with a 16-channel head–neck coil:

Anatomical imaging: T1-weighted (T1w) 3D magnetization-prepared rapid acquisition gradient-echo (TR = 2400 ms, TE = 3.24 ms, TI = 1000 ms, FA = 8°, FOV = 256 × 256 mm, voxel size = 1mm × 1mm × 1mm). 3D T2-extraction: weighted image (TR = 3200 ms, TE = 535 ms, FOV = 256 × 256 mm, voxel size = 1mm × 1mm × 1mm), a 3D fluid attenuation inversion recovery (TR = 5000ms, TE = 394ms, TI = 1600ms, FOV = 256 × 256mm, voxel size = 1mm × 1mm × 1mm).

Functional imaging: rs-fMRI EPI scans (TR = 1750 ms, TE = 30 ms, FA = 73°, FOV = 178 × 178, voxel size =2.6 mm × 2.6mm × 2.6mm, Dist. Factor 10%, volumes = 515, MB Acc Factor = 2, PAT mode GRAPPA, Acc Factor 2, phase encoding direction P>A posterior-antero) and two spin echo-EPI acquisitions with reverse phase encoding for EPI distortion correction purposes.

Structural imaging: The multi-shell dMRI protocol allows to acquire a total of 107 diffusion weighted images (DWIs) (TR/TE 4948/92 ms; voxel size 2 × 2 × 2 mm3; FOV 220 × 220 mm^2; 68 slices; multiband accelerator factor = 2, iPAT mode = 0, 7 images at b = 0 s/mm2, 8 DWIs at b value = 300 s/mm2, 32 DWIs at b value = 1000 s/mm2 and 60 DWIs at b value = 2000 s/mm2. Each diffusion direction was acquired with reverse phase encoding directions, i.e., anterior–posterior and posterior–anterior directions, for distortion correction purposes.

Perfusion imaging: pCASL with 5 post-labelling delay times (PLD = 0.5, 1, 1.5, 2, 2.5 s) (voxel size = 3.5mm × 3.5mm × 3.5mm, FOV = 224 mm, TR = 4100 ms, TE = 38.04 ms, FA = 120°, Bolus duration =700 ms, Inversion Time = 1800 ms, 4 segments).

PET attenuation correction: Ultrashort echo time (UTE) (acquired voxel size: 3mm × 3mm ×3mm, TR=4.64 ms, echo time TE=70 µs, flip angle = 10° and/or the Dixon-based deep learning approach will be used to derive MRI-based attenuation maps.

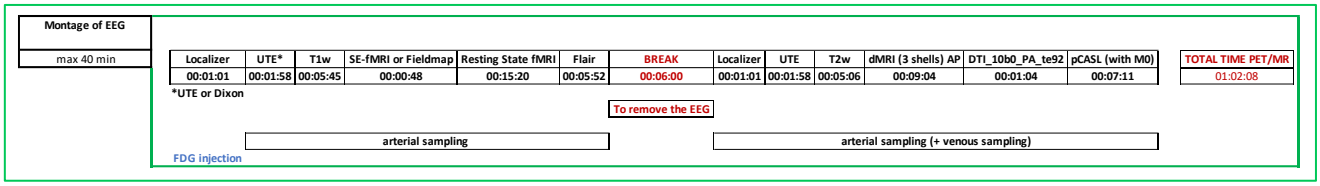

Figure 2: The full PET-MRI-EEG protocol

1.6 Harmonisation strategy

The PET and MR data are obtained in the 4 centres using the same scanner, head coil, and sequences. Therefore, the expected differences are much smaller compared to multi-centric acquisitions with different scanners. Any differences between the scanner software versions (which are minimal anyway, as they vary between two very similar versions: VE11P SP4 and VE11P SP5) will be evaluated within a harmonisation process involving “travelling heads” across 5M connectome centres.

The “travelling heads” step will allow for the evaluation of inter-site and intra-site reproducibility of MRI neuroimages as well as EEG data. The same two subjects will be imaged at the 4 different sites, and their data will be quantitatively analysed to assess inter-site reproducibility. Intra-site reproducibility will be measured with at least 2 rescans of the same subjects.

Neuroimages and EEG signals will be analysed with the same algorithms and software using the HIP platform mirrored to the WP2 infrastructure provided by INFOCAMERE, a GDPR-certified national data centre in Padova specialised in housing and hosting sensitive data from Chambers of Commerce and Private companies in Italy.

In case, to reduce the possible impact of scanner effect, the ComBat method will be used on the features already extracted from the images.