Hemispheric and Laterality Brain Age (#118913)

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1) Have any data been collected for this study already?
It's complicated. We have already collected some data but explain in Question 8 why readers may consider this a valid pre-registration nevertheless.

2) What's the main question being asked or hypothesis being tested in this study?
Hemispheric brain age (brain age estimates from a single hemisphere)
1) Brain age estimates depend on the hemisphere features are extracted from, as well as the modality (T1-weighted (T1-w), diffusion MRI (dMRI), their combination), and the hemisphere-modality interaction.
2) Handedness and the handedness-hemisphere interaction influence hemispheric brain age estimates.

Laterality brain age (laterality index [LI = (L-R)/(L+R)*100] applied to T1-weighted and diffusion MRI region-averaged metrics)
3) There are handedness-based differences between laterality brain age.

Difference in concepts
4) Hemispheric brain age differs from laterality brain age.

3) Describe the key dependent variable(s) specifying how they will be measured.
Brain age estimates: 1) hemispheric brain age, and 2) laterality brain age

4) How many and which conditions will participants be assigned to?
- Modalities: 3 (T1-weighted, diffusion MRI, multimodal (combination of both))
- Hemispheres: 2 (left, right)
- Handedness: 3 (left, right, ambidextrous)

5) Specify exactly which analyses you will conduct to examine the main question/hypothesis.
1) H1: To test the relationships between hemisphere, modality, and hemisphere-specific brain age predictions (hemispheric brain age) while controlling for age, sex and scanner site, we will employ mixed linear models (MLMs) of the following form: hemispheric brain age = hemisphere + modality + hemisphere * modality + sex + age + sex*age + (1|site) + (1|ID). Post-hoc group differences were observed for hemisphere, modality and their interaction.

H2: Handedness was added to the model to observe whether there are model differences between the resulting MLM: brain age[R,L] = handedness + hemisphere*handedness + hemisphere + modality + hemisphere*modality + sex + age + sex*age + (1|site) + (1|ID), and the previous model. Models will be statistically compared using $\chi 2$ test, and group differences (marginal means) will be observed for hemisphere, handedness and their interaction.

2) H3, testing the relationships between modality and laterality brain age while controlling for age, sex and scanner site, we employed the following MLM as a baseline model: laterality brain age = modality + sex + age + sex * age + (1|site) + (1|ID), to be compared with a model containing handedness: laterality brain age = handedness + modality + sex + age + sex * age + (1|site) + (1|ID) using a $\chi 2$ test. Group differences (marginal means) will be observed for handedness.

3) H4: three modality specific models will be employed: brain age = modality + sex + age + sex * age + (1|site) + (1|ID), and marginal means means for modality (laterality vs hemispheric brain age) compared.

6) Describe exactly how outliers will be defined and handled, and your precise rule(s) for excluding observations.
We will extract and process the latest batch of UK Biobank (UKB) MRI data (Sudlow et al., 2015) consisting of circa N = 50,000 participants. After an accurate evaluation, we will excluded subjects which requested withdrawl from the study and or possessed an ICD-10 diagnosis from categories F, G, I, and stroke, as well as data which does not meet our quality control standards using the YTTRIUM method (Maximov et al. 2021).

7) How many observations will be collected or what will determine sample size? No need to justify decision, but be precise about exactly how the number will be determined.
Circa N = 50.000 before exclusions. These data will be have to be matched between T1-weighted and diffusion MRI to form the multimodal data set.

8) Anything else you would like to pre-register? (e.g., secondary analyses, variables collected for exploratory purposes, unusual analyses planned?)
Existing data:

We have collected and processed data for approximately 42,000 individuals. UK Biobank data are however constantly being updated with new data. We attempt to process the latest batch in addition to the already processed data and conduct our analyses on these data.

Data processing procedure:

0.1) We average dMRI and T1-w metrics across regions using standard parcellations: John-Hopkins University atlas in FSL after estimating tract-based spacial statistics (Smith et al., 2006) for dMRI, and Freesurfer's automated pipeline for cortical reconstruction and subcortical segmentation of the T1-weighted images (Dale et al., 1999). We select only metrics which are specific to either L or R hemisphere to allow clear differentiation between hemispheres.

0.2) Brain age is estimated for each of the 9 data sets: 1) R hemisphere T1-w, 2) L hemisphere T1-w, 3) L hemisphere dMRI, 4) R hemisphere dMRI, 5) L hemisphere multimodal, 6) R hemisphere multimodal, 7) laterality index (LI) for T1-w images, 8) LIfor dMRI, 9) LI for multimodal data. LI refers here to the formula described above (collapsing 2 hemispheres) which will be used to calculate the laterality brain age. Hemispheric brain age on the other hand will be estimated from single hemispheres' raw region-averaged metrics (as described above).

0.3) Brain age will be predicted using XGBoost in Python (v3.7.1) using nested k-fold cross-validation (5 inner, 10 outer folds) and randomized search for parameter tuning with the following hyperparameter space: learning rate [0.01..0.3], 0.05 steps, max depth [3..6] 1 steps, and the number of trees [100..1000] 50-steps.

References:

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