ECOLE DOCTORALE PIERRE LOUIS DE SANTE PUBLIQUE A PARIS
EPIDEMIOLOGIE ET SCIENCES DE L'INFORMATION BIOMEDICALE

Directeur : Pierre-Yves Boëlle
Responsable pour Université de Paris : Isabelle Boutron

PROPOSITION DE SUJET DE THESE

SIGLE ET NOM DU LABORATOIRE : INSTITUT DE PSYCHIATRIE ET NEUROSCIENCES PARIS - INSERM UMR_S 1266
NOM DE L'EQUIPE : 'STROKE: FROM PROGNOSTIC DETERMINANTS AND TRANSLATIONAL RESEARCH TO PERSONALIZED INTERVENTIONS'
DIRECTEUR DE THESE : PÅVEL LINDBERG, CR-INSERM,
HDR
ADRESSE : 102-108 RUE DE LA SANTE, 75014 PARIS

TITRE DE LA THESE :
Brain age and its relation to brain connectivity and upper limb motor recovery after stroke

CO-ENCADRANT EVENTUEL : CLEMENT DEBACKER
EQUIPE DU CO-ENCADRANT : BIOMARQUEURS EN IMAGERIE : NEURO DEVELOPPEMENT ET PATHOLOGIES CEREBRALES
LABORATOIRE : INSTITUT DE PSYCHIATRIE ET NEUROSCIENCES PARIS - INSERM UMR_S 1266

PRESENTATION DU SUJET

Study context

Stroke is a leading cause of disability worldwide often leading to upper limb paresis dramatically reducing independence and quality of life (Dulyan et al. 2022; Su and Xu 2020; Grefkes and Fink 2020). Treatments remain inefficient and only half of the patients with initial hemiparesis fully recover control of hand movements and manual dexterity at 6 months after stroke (Kwakkel et al., 2003). The ability to accurately predict motor recovery post-stroke could improve targeting of neurorehabilitation interventions to patient's individual impairment profile and could help inform stroke survivors and their families on realistic expectations (Stinear 2017; Bucki, Spitz, and Baumann 2019; Haley et al. 2015). Defining predictors of motor recovery is crucial for stratification in clinical trials, which is much needed given poor results of large randomized trials using 'one-size-fits-all' interventions (Winstein et al., 2016). **Establishing the key predictors of upper limb motor recovery is thus a key challenge to improve stroke care.** Our previous research has identified initial motor and sensory impairment along with cognitive deficits as complimentary predictors of hand motor recovery after stroke (Plantin et al., 2021). However, our results failed to explain about 30-40% of the variance of motor recovery to 6 months after stroke (Plantin et al., 2021; Plantin et al., 2022). A factor that could explain additional variance is brain age. The incidence and prevalence of stroke, like other vascular diseases, increases with age (Grefkes and Fink 2020). Older age can worsen the outcome of a stroke (Zewudie et al. 2020). Aging is a universal non-modifiable risk factor for stroke and other research groups have identified age as a key predictor of upper limb motor recovery in decision tree algorithms, with patients over age 80 years showing less motor recovery (Stinear et al., 2017). Generally, studies use the measure of chronological age rather than biological age. **The chronological age of an individual does not necessarily reflect their biological age**, which can be influenced by genetics and lifestyle factors. For example, the amount of brain volume loss in late life can vary among individuals depending on factors such as education, lifestyle, and physical activity levels (Steffener et al. 2016; Egorova et al. 2019). Thus, people of the same chronological age might have different gray and white matter volume which could reflect a difference in their biological or brain age. By understanding the relationship between brain age and motor recovery post-stroke, it may be possible to identify individuals who are at risk for poor recovery and develop targeted interventions to improve outcomes. Brain age is well studied as a biomarker of normal and accelerated age-related degeneration (Franke and Gaser 2019; Wood et al. 2022). Rodent-specific brain age models have shown very close correlation between chronological age and MRI-derived brain age (Franke et al., 2016). There have been several proposals that stroke severity may be associated with accelerated brain aging (Egorova et al. 2019; Sohrabji, Bake, and Lewis 2013). Some preliminary studies have also investigated the relation between brain age and stroke recovery of cognitive and language functions: MRI-derived brain age can enhance prediction of cognitive and language impairments after stroke (Aamodt et al., 2022; Aben et al. 2021; Kristinsson et al. 2022). However, **studies on the role of brain age for the prediction of motor recovery are lacking.** A recent review has identified several sources of bias that may affect the performance of a brain age model. These include, among others, sex, body-mass index, physical exercise, substance use, and cognitive ability. For clinical samples, studies commonly examine how medication, illness duration, and symptom severity (Baecker et al 2021). An important step is therefore to study how such, and other, confounding factors influence brain age calculation in stroke.

In this PhD project we propose a series of studies to investigate the role of MRI-derived brain age on hand motor recovery in stroke. We will utilize already longitudinally collected MRIs in 89 hemiparetic stroke patients from the ProHand cohort at the Karolinska Institute in Sweden, a long-standing collaboration project (Plantin et al., 2021). We will also utilize data base of already collected MRI images and motor outcomes in N=100 stroke patients (Prof. Rosso, Sal-Petrière hospital).

Brain age at 3 weeks and 6 months after stroke will be measured using established machine learning algorithms (Cole et al., 2018). Analysis procedure is being validated in an ongoing Master2 project by Dr Raphaël Takyi (Biomedical Engineering Master, Université Paris Cité). This will establish how best to estimate brain age limiting influence of the lesion (using different imaging processing approaches) and study of neurological and MRI confounding factors. The PhD project will then focus on two key issues. First, to compare the contribution of brain age and chronological age in predictive models of motor recovery. We hypothesize that brain age, providing a more accurate measure of physiological age, will improve predictions models explaining more variance in recovery at 6 months after stroke. Second, brain age estimation will then be used to investigate age-related structural and functional connectivity changes in sensorimotor networks. This measure of brain age-related connectivity will be related to stroke recovery and we expect that it will provide additional information compared to connectivity measures established using chronological age.

Research questions addressed in this project include: (1) Is brain age consistent over time and across different MRI scans and what neurological (stroke type, treatment, co-morbidities) and MRI (time since stroke of MRI, lesion volume, lesion location) factors confound the brain age calculation? (2) Does MRI-derived brain age, compared to chronological age, improve prediction of upper limb motor recovery after stroke? (3) Since aging has dramatic consequences on manual dexterity we also ask whether brain age relates more strongly to manual dexterity and finger sensory function than chronological age? (4) Does brain age correlate with structural and functional brain connectivity in sensorimotor networks after stroke?

Methods

This project is planned in collaboration with Dr Jeanette Plantin at the Karolinska Insititute, Stockholm. Collected data from the ProHand prospective observational study will be studied (ClinicalTrials.gov identifier NCT02878304). This study characterized upper limb motor recovery in 89 patients with first-ever stroke with arm paresis (Plantin et al., 2021). Patients admitted to a subacute inpatient neurorehabilitation clinic were evaluated assessed at 3 weeks and 6 months after stroke onset. All patients participated in interdisciplinary rehabilitation. Clinical and specific sensorimotor assessments were collected at the three time points and MRI examination was performed at 3 weeks and 6 months post-stroke. In addition, brain age and its relation to recovery of manual haptics (sensory influence on finger motor control) and functional hand use will be studied in a separate cohort of 80 stroke patients followed up longitudinally (ANR funded HapticS project, data inclusion starting in Sept 2023).

Upper limb motor assessments included: clinical sensorimotor assessments: Overall dexterous grasp and release capability (i.e. dexterous hand use) was quantified with the Box and Block Test (BBT). The BBT comprises a rectangular box, separated by a partition and contains 150 wooden cubes (2.5 × 2.5 cm). The test instruction is to move as many cubes as possible during 60 s, one at a time and with one hand, from one side of the partition to the other. Unimanual arm and hand motor impairment was assessed, using the Fugl-Meyer Assessment for the upper extremity (FMA-UE) (0–60 points). Assessment of cognitive impairment was performed using the Barrow Neurological Institute Screen for Higher Cognitive function. Hand spasticity was assessed using the NeuroFlexor© method (AggeroMedTech.com) allowing for quantification of the neural component (NC) of the resistance to passive extension of wrist and finger flexor muscles. Somatosensory impairment (two-point discrimination, 2pD) was assessed with a Disc-Criminator (Dellon-McKinnon). Inability to detect a ≥12 mm separation indicated impairment.

Magnetic resonance imaging: Brain imaging was performed at baseline (T1) with an Ingenia 3.0 T MRsystem (Philips, Cambridge, MA). High-resolution T1-weighted anatomic images were acquired with turbo field echo 3-dimensional sequence: field of view 250 × 250 × 181 mm, matrix 228 × 227, slice thickness 1.2 mm, and number of slices 301 (echo time, shortest; relaxation time, shortest). T2 fluid-attenuated inversion recovery images were also acquired. Resting-state fMRI consisted of a gradient echo-planar sequence (echo time 35 milliseconds, flip angle 90°, voxel size 1.8 × 1.8 × 4 mm, repetition time 3,000 milliseconds) sensitive to blood oxygen level–dependent contrast.

Brain age calculation: processing is carried out with brainageR pipeline https://github.com/james-cole/brainageR (Cole et al., 2018; Figure 1). Confounding by stroke lesion will be avoided through an enantiomorphic algorithm to correct the lesioned brain to give an approximate structural integrity of the brain prior to onset of stroke (Kristinsson et al., 2022; Figure 2).

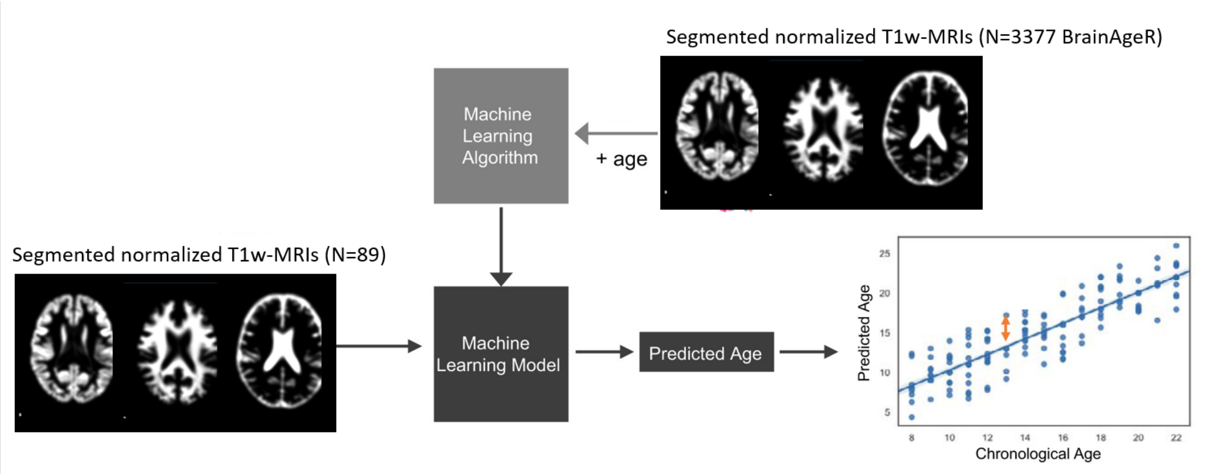

Figure 1. Scheme showing the brainageR pipeline (https://github.com/james-cole/brainageR) for calculating brain age (adapted from Diaz-Arteche and Rakesh, 2020). The machine learning algorithm was established on a data set of 3377 healthy individuals and validated in a separate sample (N=669). We will use the same algorithm on collected T1-weighted images. After segmentation and normalization using statistical parametric mapping software (SPM12) the gray and white matter and CSF are vectorized and concatenated and then a principle component analysis is used for dimensional reduction using R packages. This data is fed to model and brain age is estimated.

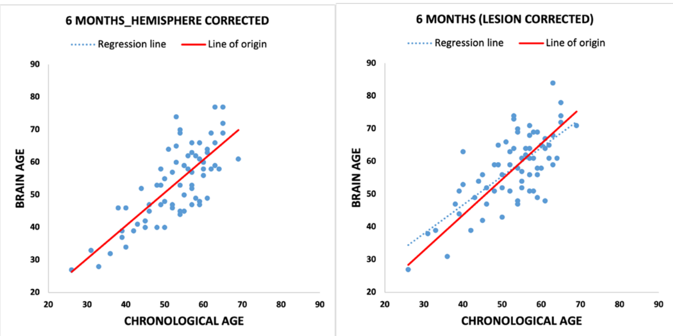

Figure 2. Preliminary brain age data vs chronological age from the ProHand cohort to compare different preprocessing of lesion. The enantiomorphic (lesioned brain tissue replaced by healthy tissue from non-affected hemisphere) corrected data on left provided slightly superior correlation with chronological age. Another approach using only the non-lesioned hemisphere will be developed and tested.

Statistical analysis:. The feasibility of this project and the sample size power calculation of the number of patients to include are based on data from a pilot analysis (part of M2 project) and recent results showing how brain age predicts aphasia recovery after stroke (Kristinsson et al., 2022). A pilot linear regression analysis, on N=71 stroke patients in our lab, revealed that chronological age relates negatively with motor outcome, measured using Fugl-Meyer scale, with R=-0.16. The brain age, calculated using the method proposed in this project, showed a stronger negative correlation with motor outcome R=-0.36.

These values were similar with values reported by Kristinsson et al (2022) regarding how chronological and brain age measures correlate negatively with aphasia recovery after stroke. We performed a power calculation using refined Fischer Z algorithm on the one-tailed hypothesis that Rho_ChronologicalAge <= Rho_BrainAge using the previously mentioned pilot results. A sample size of 137 patients was required to achieve 0.9 statistical power with type I error rate at 0.05.
To ensure sufficient statistical power we will collaborate with Prof. Charlotte Rosso at the Neurovascular Department at the Pitié-Sal-Petrière hospital. Prof. Rosso has T1-weighted images and motor outcome data collected in 100 stroke patients at 6-months after stroke. Moreover, together with Prof David Calvet we expect to have access to anatomical MRIs (3D T1 images) in 200 stroke patients with lacunar infarcts that have been followed up longitudinally in Neurology Depts. of Laribosière and GHU Sainte-Anne hospitals (DHU-LAC cohort study led by Prof Eric Jouvent; approval from study committee in preparation).
Finally, multi-variate linear regression analysis will be performed to investigate how brain age can enhance prediction of motor recovery after stroke. The model will include lesion volume, age and initial motor status after stroke. Variables with R>0.1 in univariate regression will be included in multivariable regression analysis with forward stepwise procedure for selection of predictors. Independent variables will be carried forward in order of univariate association strength (i.e., the highest R2).

Ethical considerations: the ProHand study including MRI analysis was approved by the Regional Ethical Review Board in Stockholm (DNR 2011/1510-31/3). The studies from Prof Rosso has also been approved by the regional ethics board (CPP).

Other requested funding: this brain age study has not been funded by other sources.

Planning:
Sept 2023 –Feb 2024: analysis and write-up of paper I. Raphael will reinforce learning of neuroimaging analysis (preprocessing comparisons using SPM12, FSL and python scripts) and learn to perform statistical analysis using R. The neuroimaging analysis is performed in close collaboration with the team of Prof. Catherine Oppenheim (IPNP, Inserm U1266) and with research engineer Clément Debacker who will be Raphael's co-supervisor for the PhD.
March 2024 –Aug 2024: Raphael will learn to analyze structural and functional brain connectivity. Diffusion weighted imaging will be analyzed using FSL software and white matter connectivity maps will be obtained. Resting-state functional MRI sequences will be used to probe functional brain connectivity and analysis will be performed using SPM12 and python scripts. Raphael will attend a course on statistical parametric mapping (SPM) and FSL tools.
Sept 2024 – Feb 2025: write-up of scientific publication (paper II) on brain-age connectivity post-stroke and its relation to motor recovery.

March 2025 – April 2025: analysis of confounding factors and longitudinal changes of brain age calculation in stroke. Learning of additional statistical analysis tools for evaluation of confounding factor influence through collaboration with research engineer Sylvain Charron in Pr Oppenheim's team.
May 2025 – Aug 2025: brain age analysis in separate HapticS cohort and analysis of relation to manual haptics and functional hand recovery after stroke. Write-up of paper IV.
Sept 2025 – Feb 2026: write-up of paper III on confounding factors and longitudinal changes of brain age calculation in stroke.
March 2026 – Aug 2026: communication of results at international conference and write-up of thesis.
Sept 2026: public defense of thesis

Planned publications:

- Article 1: Brain age and predicition of hand motor recovery after stroke
- Article 2: The structural and functional connectivity correlates of brain age in stroke
- Article 3: Clinical and MRI confounding factors of brain age estimation and brain age changes between 3 weeks and 6 months after stroke
- Article 4: Brain age and its relation to recovery of manual haptics and functional hand use in stroke

References

Aamodt EB, Alnaes D, de Lange AM, Aam S, Schellhorn T, Saltvedt I, Beyer MK, Westlye LT. 2022. "Longitudinal Brain Age Prediction and Cognitive Function after Stroke." https://doi.org/10.1101/2022.03.18.22272556.

Aben HP, de Munter L, Reijmer YD, Spikman JD, Johanna M.A. Visser-Meily, Geert JB, Paul LMK. 2021. "Prediction of Cognitive Recovery after Stroke: The Value of Diffusion-Weighted Imaging-Based Measures of Brain Connectivity." Stroke, 1983–92. https://doi.org/10.1161/STROKEAHA.120.032033.

Baecker L, Garcia-Dias R, Vieira S, Scarpazza C, Mechelli A. 2021. "Machine learning for brain age prediction: Introduction to methods and clinical applications." EBioMedicine, 72, 103600.

Bucki B, Elisabeth S, Michèle B. 2019. "Emotional and Social Repercussions of Stroke on Patient-Family Caregiver Dyads: Analysis of Diverging Attitudes and Profiles of the Differing Dyads." PLoS ONE. Public Library of Science. https://doi.org/10.1371/journal.pone.0215425.

Díaz-Arteche C, & Rakesh D. 2020. Using neuroimaging to predict brain age: insights into typical and atypical development and risk for psychopathology. Journal of Neurophysiology, 124(2), 400-403.

Dulyan L, Lia T, Valentina P, Maurizio C, Stephanie JF, Michel Thiebaut S. 2022. "Longitudinal Prediction of Motor Dysfunction after Stroke: A Disconnectome Study." Brain Structure and Function, December. https://doi.org/10.1007/s00429-022-02589-5.

Egorova N, Franziskus L, Vladimir H, Amy B. 2019. "Predicted Brain Age After Stroke." Frontiers in Aging Neuroscience 11 (December). https://doi.org/10.3389/fnagi.2019.00348.

Franke K, Christian G. 2019. "Ten Years of Brainage as a Neuroimaging Biomarker of Brain Aging: What Insights Have We Gained?" Frontiers in Neurology. Frontiers Media S.A.https://doi.org/10.3389/fneur.2019.00789.

Franke K, Dahnke R, Clarke G, Kuo A, Li C, Nathanielsz P, et al. 2016. "MRI based biomarker for brain aging in rodents and non-human primates." International Workshop on Pattern Recognition in Neuroimaging (PRNI).

Grefkes C, Gereon RF. 2020. "Recovery from Stroke: Current Concepts and Future Perspectives." Neurological Research and Practice 2 (1). https://doi.org/10.1186/s42466-020-00060-6.

Haley WE, David LR, Martha H, Olivio JC. 2015. "Long-Term Impact of Stroke on Family Caregiver Well-Being A Population-Based Case-Control Study."

Kelly-Hayes M. 2010. "Influence of Age and Health Behaviors on Stroke Risk: Lessons from Longitudinal Studies." Journal of the American Geriatrics Society. https://doi.org/10.1111/j.1532-5415.2010.02915.x.

Kristinsson S, Natalie B, Christopher R, Roger N, Dirk BO, Sigridur M, Haukur H, et al. 2022. "Brain Age Predicts Long-Term Recovery in Post-Stroke Aphasia." Brain Communications 4 (5). https://doi.org/10.1093/braincomms/fcac252.

Rost NS, Alex B, Jin ML, Marc R, Steven M, Louise S, Vincent T, et al. 2016. "Stroke Severity Is a Crucial Predictor of Outcome: An International Prospective Validation Study." Journal of the American Heart Association 5 (1): 1–7. https://doi.org/10.1161/JAHA.115.002433.

Sohrabji F, Shameena B, Danielle KL. 2013. "Age-Related Changes in Brain Support Cells: Implications for Stroke Severity." Neurochemistry International. Elsevier Ltd. https://doi.org/10.1016/j.neuint.2013.06.013.

Stanescu IC, Angelo C. Bulboaca GBD, Gabriel G, Dana MF. 2019. "Predictors for Early Motor Improvement in Patients with Ischemic Stroke." Balneo Research Journal 10 (Vol.10, No.3): 236–42. https://doi.org/10.12680/balneo.2019.263.

Steffener J, Christian H, Deirdre OS, Qolamreza R, Louis B, Yaakov S. 2016. "Differences between Chronological and Brain Age Are Related to Education and Self-Reported Physical Activity." Neurobiology of Aging 40 (April): 138–44. https://doi.org/10.1016/j.neurobiolaging.2016.01.014.

Stinear C. 2017. "Prediction of Motor Recovery after Stroke: Advances in Biomarkers." Vol. 16. www.thelancet.com/neurology.

Su F, Wendong X. 2020. "Enhancing Brain Plasticity to Promote Stroke Recovery." Frontiers in Neurology. Frontiers Media S.A. https://doi.org/10.3389/fneur.2020.554089.

Winstein CJ, Wolf SL, Dromerick AW, Lane CJ, Nelsen MA, Lewthwaite R, Azen SP. (2016). Effect of a task-oriented rehabilitation program on upper extremity recovery following motor stroke: the ICARE randomized clinical trial. Jama, 315(6), 571-581.

Wood DA, Sina K, Ayisha B, Emily G, Antanas M, Jeremy L, Matthew T, et al. 2022. "Accurate Brain-age Models for Routine Clinical MRI Examinations." NeuroImage 249 (April). https://doi.org/10.1016/j.neuroimage.2022.118871.

Zewudie AZ, Tolcha R, Solomon H, Dejen N, Yitagesu M, Temesgen A, Desalegn F, Tewodros Y. 2020. "Treatment Outcome and Its Determinants among Patients Admitted to Stroke Unit of Jimma University Medical Center, Southwest Ethiopia." Stroke Research and Treatment 2020. https://doi.org/10.1155/2020/8817948.

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SPECIALITE DE LA THESE

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Santé publique - Epidémiologie sociale	☐
Santé publique - Epidémiologie génétique	☐
Santé publique - Biostatistique	☐
Santé publique - Biomathématiques	☐
Santé publique - Biostatistique et Biomathématiques	☐
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