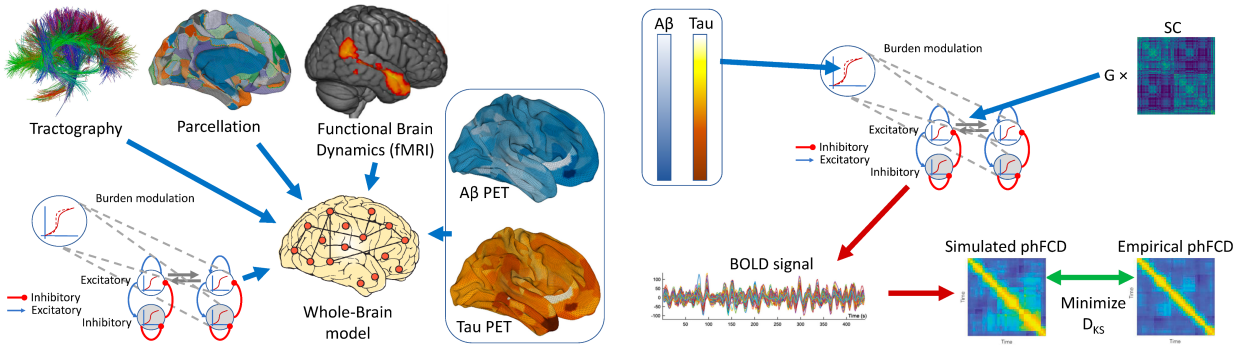
Differential Influences of Amyloid-Beta and Tau in Alzheimer's Disease through Whole-Brain Modeling

Gustavo Patow[1,4], Leon Stefanovski[2,3], Petra Ritter[2,3], Gustavo Deco[4] and Xenia Kobeleva[5,6], for the Alzheimer's Disease Neuroimaging Initiative*

[1]ViRVIG, Universitat de Girona, Girona, 17003 Spain. Contact: gustavo.patow@udg.edu
[2]Berlin Institute of Health at Charité – Universitätsmedizin Berlin, Berlin, 10115 Germany
[3]Department of Neurology with Experimental Neurology, Brain Simulation Section, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, 10115 Germany
[4]Center for Brain and Cognition, Computational Neuroscience Group, Department of Information and Communication Technologies, Universitat Pompeu Fabra, Barcelona, 08005 Spain
[5]University Hospital Bonn, Clinic for Neurology, Bonn, Germany
[6]German Center for Neurodegenerative Diseases (DZNE) Bonn, Bonn, 53105 Germany

Introduction:
Alzheimer's Disease is a neurodegenerative condition associated with the accumulation of two misfolded proteins, amyloid-beta (Aβ) and tau [Busche, Hyman 2020]. We use whole-brain modeling techniques to study the impact of both Aβ and tau on the dynamics of regional behaviors in AD, discerning the impact of each protein in isolation and in combination, and being able to assess their relative weights on contributing to abnormal brain activity, and going beyond previous approached that only focused on a single type of burden [Stefanovski et al. 2021].

Methods:
We use the Balanced Dynamic Mean Field (BEI) model [Deco et al. 2014], which can reproduce the fMRI activity based on interactions of excitatory and inhibitory neural populations interconnected by white matter tracts. In this model, local (i.e., regional) dynamics are driven by the interactions between these populations, and with the net output of other areas, as mediated by the anatomical connectivity matrix. We use this model to find the optimal parameters that best describe the effects of Aβ and tau on the excitation-inhibition balance of the local nodes.



Results:
We found a clear dominance of Aβ over tau in the early disease stages (Mild Cognitive Impairment, MCI), while the protein tau dominates over Aβ in the latest stages (manifest dementia, AD). We identify crucial roles for Aβ and tau in complex neuronal dynamics and demonstrate the viability of using regional distributions to define models of large-scale brain function in AD.

Discussion:
Our study provides further insight into the dynamics and complex interplay between these two proteins, opening the path for further investigations on biomarkers and candidate therapeutic targets in-silico.

Bibliography:
[Busche-Hyman 2020] Busche Marc Aurel, Hyman Bradley T.. Synergy between amyloid-β and tau in Alzheimer's disease Nature Neuroscience. 2020;23:1183–1193.
[Deco et al. 2014] Deco Gustavo, Ponce-Alvarez Adrian, Hagmann Patric, Romani Gian Luca, Mantini Dante, Corbetta Maurizio. How Local Excitation–Inhibition Ratio Impacts the Whole Brain Dynamics Journal of Neuroscience. 2014;34:7886–7898.
[Stefanovski et al. 2021] Stefanovski Leon, Meier Jil Mona, Pai Roopa Kalsank, et al. Bridging Scales in Alzheimer's Disease: Biological Framework for Brain Simulation With The Virtual Brain Frontiers in Neuroinformatics. 2021;15.

Acknowledgments:
This research was partially funded by Grant PID2021-122136OB-C22 funded by MCIN/AEI/10.13039/501100011033 and by ERDF A way of making Europe of **GP**. This work was supported by an add-on fellowship of the Joachim Herz Foundation of **XK**. **PR** had the support of the following grants: H2020 Research and Innovation Action Grant Human Brain Project SGA2 785907 (PR), H2020 Research and Innovation Action Grant Human Brain Project SGA3 945539 (PR), H2020 Research and Innovation Action Grant Interactive Computing E-Infrastructure for the Human Brain Project ICEI 800858 (PR), H2020 Research and Innovation Action Grant EOSC VirtualBrainCloud 826421 (PR), H2020 Research and Innovation Action Grant AISN 101057655 (PR), H2020 Research Infrastructures Grant EBRAINS-PREP 101079717 (PR), H2020 European Innovation Council PHRASE 101058240 (PR), H2020 Research Infrastructures Grant EBRAIN-Health 101058516 (PR), H2020 European Research Council Grant ERC BrainModes 683049 (PR), JPND ERA PerMed PatternCog 2522FSB904 (PR), Berlin Institute of Health & Foundation Charité (PR), Johanna Quandt Excellence Initiative (PR), German Research Foundation SFB 1436 (project ID 425899996) (PR), German Research Foundation SFB 1315 (project ID 327654276) (PR), German Research Foundation SFB 936 (project ID 178316478) (PR), German Research Foundation SFB-TRR 295 (project ID 424778381) (PR), German Research Foundation SPP Computational Connectomics RI 2073/6-1, RI 2073/10-2, RI 2073/9-1 (PR).