



# eBRAIN-Health

## Public report

## D9.1 Demonstrator Disease Prediction

Project number	<b>101058516</b>
Project title	<b>eBRAIN-Health - Actionable Multilevel Health Data</b>
Submission date	<b>July 2024</b>
Authors	<b>Leon Stefanovski and Petra Ritter (CHARITE)</b>
Dissemination level	<b>Public (PU)</b>
Public project website	<b><a href="https://ebrain-health.eu/">https://ebrain-health.eu/</a></b>



Funded by  
the European Union

## Table of content

1. eBRAIN-Health .....	3
2. eBRAIN-Health consortium .....	3
3. Introduction .....	4
4. Partners involved .....	5
5. Description of work performed .....	5
6. Results.....	6
7. Conclusion, next steps .....	7
8. Figures and Tables .....	8
9. Acknowledgements .....	9
10. Bibliography .....	9

## 1. eBRAIN-Health

The Project eBRAIN-Health is a collaborative effort that aims to establish a comprehensive distributed research platform designed to model and simulate the complex neurobiological phenomena underlying human brain function and dysfunction, all within a data protection-compliant environment. This ambitious initiative, which you are a part of, will provide access to thousands of multilevel virtual brains derived from patients and healthy controls, facilitating significant advances in research and innovation. By preprocessing brain data from various sources, eBRAIN-Health seeks to tackle the grand societal challenge of dementia through a collaborative and interdisciplinary approach. Central to this effort is creating a digital twin for dementia, which will model and simulate intricate neurobiological processes, serving as a critical resource for research infrastructure communities. The eBRAIN-Health-Cloud will offer comprehensive end-to-end services for personalized brain modeling and simulations across distributed e-infrastructures, ensuring data protection by design and default. This includes providing simulation-ready, multiscale brain data that span molecular (genomics, proteomics, metabolomics) and cellular levels through electrophysiology, imaging, behavioral, clinical, lifestyle, environmental data, and data from wearables. All brain data will be preprocessed and annotated to relate to a standard reference 3D brain space, enhancing their utility and accessibility.

Alzheimer's disease (AD) exemplifies the urgent need for such an advanced platform. As a leading cause of dementia, AD affects millions globally, with its incidence expected to rise sharply as populations age. Current diagnostic methods and treatments are limited, and the disease is often unable to be detected at early stages or halt its progression effectively. This underscores the necessity for innovative approaches in AD research. The eBRAIN-Health platform aims to bridge this gap by providing tools that can predict disease onset and progression through advanced modeling and simulation techniques. By integrating diverse data types — ranging from molecular signatures to clinical assessments and neuroimaging — researchers can gain a more holistic understanding of AD pathophysiology and identify potential biomarkers for early detection and targeted therapy.

## 2. eBRAIN-Health consortium

- CHARITE – Universitaetsmedizin Berlin, Germany
- EBRAINS, Belgium
- Forschungszentrum Juelich GmbH, Germany
- Stichting Radboud Universiteit, Netherlands
- Universidad Pompeu Fabra, Spain
- OSLO Universitetssykehus, Norway
- tp21 GMBH, Germany
- Fraunhofer Gesellschaft zur Foerderung der Angewandten Forschung eV, Germany
- INDOC RESEARCH EUROPE gGmbH, Germany
- Universitaet Wien, Austria
- Universidad Complutense de Madrid, Spain
- EODYNE Systems SL, Spain
- ATHENA – Research and Innovation Center, Greece
- University of Oslo, Norway
- Universita degli Studi di Roma la Sapienza, Italy
- Alzheimer Europe, Luxembourg
- Institute National de Recherche en Informatique et Automatique, France
- Centre Hospitalier Universitaire Vaudois, Switzerland

- The University of Edinburgh, United Kingdom

[Find the partners on our website](#)

### 3. Introduction

AD represents a profound public health challenge due to its escalating incidence, unclear etiopathogenesis, and the significant socioeconomic burden it imposes. The global cost associated with dementia, which includes AD, is estimated to surpass \$1 trillion annually, reflecting not only direct medical expenses but also the profound indirect costs related to caregiving and lost productivity (Wimo, Guerchet et al. 2017). The prevalence of AD is increasing with the aging population, thereby amplifying its societal impact. The pathophysiology of Alzheimer's remains enigmatic, involving complex interactions between genetic, environmental, and lifestyle factors, which complicates the development of definitive diagnostic and therapeutic strategies. Current treatments, such as cholinesterase inhibitors and NMDA receptor antagonists, besides recent Anti-Amyloid-beta-treatments (van Dyck, Swanson et al. 2022), offer only marginal symptomatic relief without altering the disease course (Cummings, Lee et al. 2021).

Early and accurate prediction of AD is crucial not only for timely diagnosis but also for the stratification of patients in clinical trials aimed at assessing the efficacy of potential treatments. Precision medicine approaches necessitate the identification of pathological subgroups within the heterogeneous AD population to tailor individualized treatment strategies (Hampel, Toschi et al. 2018). Diagnostic methodologies have advanced, leveraging clinical examinations, neuroimaging, and fluid biomarkers to identify AD even at the preclinical stage. For instance, recent advancements in artificial intelligence (AI) applications in MRI have shown promise in enhancing diagnostic accuracy. AI-driven analysis of structural MRI can detect subtle brain changes associated with AD, providing a non-invasive and accessible tool for early diagnosis (Falahati, Westman et al. 2014). Additionally, blood biomarkers such as phosphorylated tau at threonine 181 (pTau181) have emerged as reliable indicators of AD pathology, correlating well with neurofibrillary tangles observed in the brain (Thijssen, La Joie et al. 2020).

The imperative now extends beyond mere diagnosis to predicting functional outcomes based on underlying pathology. The ability to forecast cognitive and functional decline from specific pathological markers can revolutionize AD management by enabling proactive interventions. The integration of multimodal neuroimaging techniques provides a comprehensive understanding of AD pathology. Structural MRI offers detailed anatomical insights, diffusion-weighted imaging (DWI) elucidates structural connectivity, and functional MRI (fMRI) captures brain activity and dynamic functional connectivity. Positron emission tomography (PET) with tracers for amyloid-beta, tau, and fluorodeoxyglucose (FDG) further enriches this multimodal approach by highlighting specific pathological features (Jack, Bennett et al. 2018). Electrophysiological methods like electroencephalography (EEG) and magnetoencephalography (MEG) contribute additional layers of data on brain function and connectivity.

Our study utilized a balanced Excitation-Inhibition (EI) model incorporating amyloid-beta and tau pathology data derived from PET scans in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. These models were employed to predict individual functional connectivity (FC) and dynamic functional connectivity (dFC). An overview about the experimental design can be found in **Figure 1**. Our results demonstrate that amyloid-beta and tau pathologies can predict multimodal functional data

across the AD spectrum. Specifically, amyloid-beta pathology alone is a robust predictor of functional data in cognitively normal individuals and those with mild cognitive impairment (MCI). In contrast, tau pathology predominantly predicts functional data in individuals with AD. This predictive capability underscores the potential of integrating PET-derived pathological markers with advanced neuroimaging techniques to anticipate functional outcomes in AD.

In conclusion, the integration of neuroimaging modalities and (potentially) fluid biomarkers with sophisticated predictive models holds immense promise for advancing our understanding of Alzheimer's disease. This approach not only facilitates early and accurate diagnosis but also enables the prediction of functional decline, thereby informing individualized treatment strategies. Continued research and validation of these predictive models in more extensive, diverse cohorts are essential to realize their full potential in clinical practice. The future of AD management is bright, thanks to such interdisciplinary and technologically advanced methodologies, which promise to revolutionize Alzheimer's disease management and mitigate its devastating impact on individuals and society.

#### 4. Partners involved

Charité Universitätsmedizin Berlin – Leon Stefanovski, Petra Ritter  
Pompeu Fabra University Barcelona - Gustavo Deco

#### 5. Description of work performed

This demonstrator is based on the work by Patow et al. (Patow, Stefanovski et al. 2023), which was performed as part of the eBrain-Health symposium. The study is published under open access conditions according to a CC-BY 4.0 license, which allows the reproduction in this report. For details on the license, please refer to <https://creativecommons.org/licenses/by/4.0/>.

The presented study utilized empirical data from the ADNI to include healthy controls (HC), mild cognitive impairment (MCI) patients, and Alzheimer's disease (AD) patients. Participants underwent structural MRI to create a brain parcellation using the Human Connectome Project (HCP) minimal preprocessing pipeline. PET imaging data for amyloid-beta ( $A\beta$ ) and tau were processed to derive regional burden values using ADNI's preprocessed AV-45 and AV-1451 tracers. Diffusion-weighted imaging (DWI) was processed with MRtrix3 (Tournier, Smith et al. 2019) to generate structural connectomes.

A balanced excitation-inhibition (BEI) model was employed to simulate neural dynamics, incorporating excitatory and inhibitory neural populations interconnected by white matter tracts. The model integrated structural connectivity from DWI, functional connectivity from fMRI, and protein burden data from PET to simulate brain dynamics. The global coupling parameter  $G$  was optimized to fit the BEI model to empirical fMRI data, focusing on static functional connectivity (FC), sliding-window functional connectivity dynamics (swFCD), and phase functional connectivity dynamics (phFCD). Optimal fitting was achieved using the Kolmogorov-Smirnov (KS) distance to compare empirical and simulated phFCD matrices.

Regional distributions of  $A\beta$  and tau were incorporated into the model to modulate the local gain parameter  $M(E,I)$  for each neuronal population. Bayesian optimization using Gaussian processes was employed to fit the model parameters, addressing potential local minima issues in traditional

optimization methods. The impact of  $A\beta$  and tau on neural dynamics was evaluated individually and in combination. Empirical burden densities were compared with randomly shuffled densities to assess model performance. The influence of each protein burden was assessed by optimizing them in isolation and comparing results with the combined model.

The model was validated by fitting it to empirical fMRI data from HC, MCI, and AD cohorts, showing distinct impacts of  $A\beta$  and tau at different disease stages. This comprehensive approach integrates multimodal imaging data to predict functional brain changes in Alzheimer's disease by modeling the causal impact of protein burdens on neural dynamics.

## 6. Results

As a result, we first evaluated the homogeneous BEI model's ability to replicate the empirical properties of resting-state FC) data. The global coupling parameter  $G$  was optimized without considering heterogeneity, setting all regional gain parameters  $M(E,I) = 1$ . The model's performance was assessed by its ability to reproduce edge-level static FC, sliding-window functional connectivity dynamics swFCD, and phFCD. The phFCD was found to be the most stringent constraint on the model, leading to an optimal  $G$  value of 3.1, which was used for further fitting procedures.

After determining the global coupling parameter, regional heterogeneity in the distributions of  $A\beta$  and tau was introduced. Introducing these protein burdens aimed to represent neural dynamics better and improve the fitting of phFCD. The study found distinct impacts of  $A\beta$  and tau across different cohorts:  $A\beta$  showed a significant effect in early disease stages (i.e., MCI), while tau had a more substantial influence in later stages (i.e., AD). For HC subjects,  $A\beta$  already played an important role, although with less difference between the combined  $A\beta$  and tau model and  $A\beta$  in isolation.

An analysis based on the AT(N) classification (Jack, Bennett et al. 2018) grouped subjects into four categories: A-T-, A+T-, A-T+, and A+T+. The results showed similar behaviors for the A-T- group compared to the HC group and for the A+T+ group compared to the AD group. However, the small number of subjects in the A-T+ and A+T- groups led to mixed or inconclusive results. For details, see **Figure 2**.

The impact of protein burdens was further analyzed by optimizing the model parameters and simulating the dynamical model multiple times for each subject. The results demonstrated that the combined action of  $A\beta$  and tau provided the best performance, outperforming the homogeneous model. The combined burden significantly improved ( $p < 0.0004$ ) across all cohorts. For AD subjects, tau alone had a more substantial influence, while for MCI subjects,  $A\beta$  played a more dominant role. The differences between the combined burden and  $A\beta$  or tau alone were assessed, with the combined burden showing statistically significant improvements in most cases.

The study validated the model by fitting it to empirical fMRI data from HC, MCI, and AD cohorts, highlighting the distinct impacts of  $A\beta$  and tau at different disease stages. The heterogeneous model incorporating regional information on protein burdens more faithfully reproduced empirical properties of dynamic brain activity than the homogeneous model with fixed parameters.

## 7. Conclusion, next steps

In summary, this demonstrator elucidates the predictive capacity of functional properties in Alzheimer's disease (AD) based on its underlying pathology, highlighting the roles of A $\beta$  and tau proteins. Our findings indicate that both A $\beta$  and tau can predict multimodal functional data across the entire spectrum of AD, with A $\beta$  being more predictive in controls and MCI cases and tau being more predictive in established AD. This raises the question of whether cerebrospinal fluid (CSF) or serum biomarkers could offer similar predictive capabilities, contingent on finding a suitable proxy for the spatial distribution of these biomarkers.

The results underscore the importance of A $\beta$  and tau in predicting functional impairments and suggest the potential for extending these predictions to behavioral levels. Future work will validate this concept using other data modalities in the eBRAIN-Health project, such as MEG, behavioral data, and CSF and serum biomarkers. Additionally, it is essential to validate the functional predictions against long-term outcomes, including disease progression and treatment effectiveness, to implement these findings in future clinical trial designs.

Our research illustrates that A $\beta$  and tau are critical in early disease stages and play a significant role in advanced stages, confirming their importance in disease progression. The observed dominance of A $\beta$  in MCI and tau in AD suggests distinct pathological mechanisms at different stages of the disease, corroborating findings from previous studies that demonstrate a complex interplay between these proteins in driving neurodegeneration. This differential impact emphasizes the need for stage-specific therapeutic strategies and supports the potential for using these biomarkers in personalized medicine.

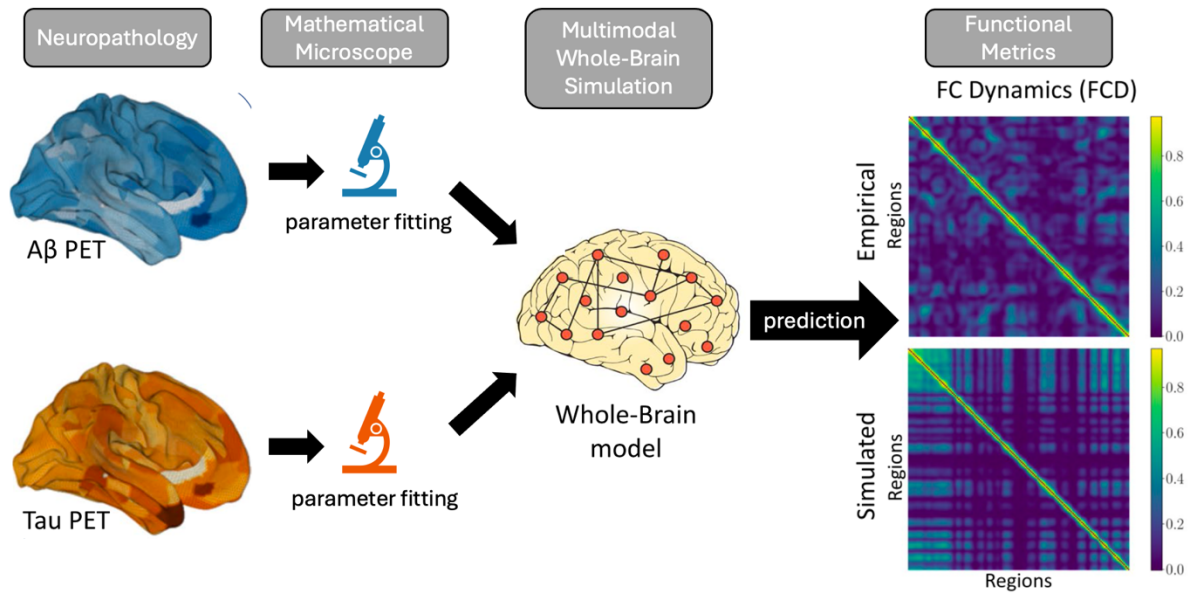
Furthermore, the study raises the possibility of using CSF and serum biomarkers to predict functional data, a promising avenue to enhance early diagnosis and monitoring of AD. By finding appropriate proxies for spatial distribution, these fluid biomarkers could offer a less invasive alternative to current imaging techniques, making routine screening more feasible and widespread.

The following steps in this research will focus on validating the proposed model with additional data modalities. MEG offers a high temporal resolution that can capture dynamic brain activity, providing further insights into the functional implications of A $\beta$  and tau distributions. Behavioral data will help link neural changes to cognitive and functional outcomes, enhancing our understanding of how these pathological processes manifest clinically. Integrating CSF and serum biomarkers with imaging data could also refine our model, leading to more accurate predictions and a better understanding of disease mechanisms.

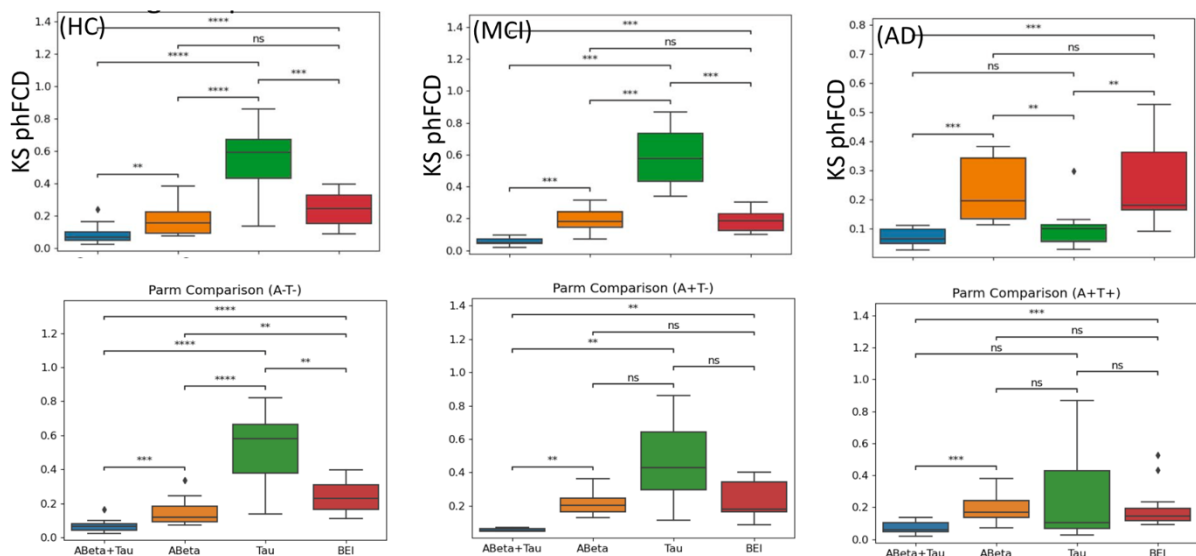
To ensure the robustness and applicability of our model, we will validate its predictions against long-term outcomes such as disease progression and treatment effectiveness. This validation is crucial for translating our findings into clinical practice, where they can inform the design of future clinical trials and therapeutic interventions. Implementing this model in clinical trial designs will allow for more targeted and efficient testing of new treatments, ultimately improving patient care and outcomes.

In conclusion, this study demonstrates the feasibility and potential of using whole-brain modeling to predict functional properties in AD from underlying pathology. By leveraging the spatial distributions of A $\beta$  and tau, our model provides a detailed and dynamic representation of how these proteins influence brain function across different stages of the disease. This approach enhances our understanding of AD pathophysiology. It opens new avenues for early diagnosis, monitoring, and treatment, paving the way for more effective and personalized therapeutic strategies in the fight against Alzheimer's disease.

## 8. Figures and Tables



**Figure 1.** Workflow illustrating the experimental design. We use of PET imaging to assess A $\beta$  and Tau neuropathology and explore their influence by parameter fitting, acting as a mathematical microscope that can quantify the influence of both protein pathology. Subsequently, a whole-brain simulation with a balanced Excitation-Inhibition model, based on structural connectivity, is used to predict functional connectivity dynamics (FCD) as a surrogate for the functional outcome based on protein pathology. Thus, the pipeline allows to quantify the actual mechanistic influence of A $\beta$  and Tau on an individual level in order to derive functional from structural data patterns. This figure contains modified elements from (Patow, Stefanovski et al. 2023), which is published under open access conditions according to a CC-BY 4.0 license: <https://creativecommons.org/licenses/by/4.0/>.



**Figure 2.** Box plots depicting the KS phFCD (Kolmogorov-Smirnov distance between empirical and simulated phase functional connectivity dynamics) values for different subject groups (HC, MCI, AD) and parameter comparisons (A-T-, A+T-, A+T+). Each subplot shows the distribution of KS phFCD across different conditions: A $\beta$  and Tau, only A $\beta$ , only Tau, and the original balanced Excitation-Inhibition model without further perturbation (BEI). Statistical significance is indicated by asterisks, with ns

indicating no significance, \* for  $p < 0.05$ , \*\* for  $p < 0.01$ , \*\*\* for  $p < 0.001$ , and \*\*\*\* for  $p < 0.0001$ . As it can be seen, the combined model outperforms all others in each condition. Meanwhile, the AD pHFC can also be explained well by a Tau-only model, while HC and MCI can be explained well with A $\beta$ -only. Interestingly, the same trends can be observed for the corresponding biomarker categories A-T-, A+T-, and A+T+, suggesting an imminent mechanism which can be observed both in clinical and in biomarker-based stratifications. This figure contains modified elements from (Patow, Stefanovski et al. 2023), which is published under open access conditions according to a CC-BY 4.0 license: <https://creativecommons.org/licenses/by/4.0/>.

## 9. Acknowledgements

The authors acknowledge the use of OpenAI's ChatGPT-4o for assistance in language editing, which has been used in order to improve the clarity and readability of the manuscript. The content of this report lies in the sole responsibility of the authors.

## 10. Bibliography

Cummings, J., G. Lee, K. Zhong, J. Fonseca and K. Taghva (2021). "Alzheimer's disease drug development pipeline: 2021." Alzheimer's & Dementia: Translational Research & Clinical Interventions **7**(1): e12179.

Falahati, F., E. Westman and A. Simmons (2014). "Multivariate data analysis and machine learning in Alzheimer's disease with a focus on structural magnetic resonance imaging." J Alzheimers Dis **41**(3): 685-708.

Hampel, H., N. Toschi, C. Babiloni, F. Baldacci, K. L. Black, A. L. W. Bokde, R. S. Bun, F. Cacciola, E. Cavedo, P. A. Chiesa, O. Colliot, C. M. Coman, B. Dubois, A. Duggento, S. Durrleman, M. T. Ferretti, N. George, R. Genthon, M. O. Habert, K. Herholz, Y. Koronyo, M. Koronyo-Hamaoui, F. Lamari, T. Langevin, S. Lehericy, J. Lorenceau, C. Neri, R. Nisticò, F. Nyasse-Messene, C. Ritchie, S. Rossi, E. Santarnecchi, O. Sporns, S. R. Verdooner, A. Vergallo, N. Villain, E. Younesi, F. Garaci and S. Lista (2018). "Revolution of Alzheimer Precision Neurology. Passageway of Systems Biology and Neurophysiology." J Alzheimers Dis **64**(s1): S47-s105.

Jack, C. R., Jr., D. A. Bennett, K. Blennow, M. C. Carrillo, B. Dunn, S. B. Haeberlein, D. M. Holtzman, W. Jagust, F. Jessen, J. Karlawish, E. Liu, J. L. Molinuevo, T. Montine, C. Phelps, K. P. Rankin, C. C. Rowe, P. Scheltens, E. Siemers, H. M. Snyder, R. Sperling, C. Elliott, E. Masliah, L. Ryan and N. Silverberg (2018). "NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease." Alzheimer's & Dementia: The Journal of the Alzheimer's Association **14**(4): 535-562.

Patow, G., L. Stefanovski, P. Ritter, G. Deco, X. Kobeleva and I. for the Alzheimer's Disease Neuroimaging (2023). "Whole-brain modeling of the differential influences of amyloid-beta and tau in Alzheimer's disease." Alzheimer's Research & Therapy **15**(1): 210.

Thijssen, E. H., R. La Joie, A. Wolf, A. Strom, P. Wang, L. Iaccarino, V. Bourakova, Y. Cobigo, H. Heuer, S. Spina, L. VandeVrede, X. Chai, N. K. Proctor, D. C. Airey, S. Shcherbinin, C. Duggan Evans, J. R. Sims, H. Zetterberg, K. Blennow, A. M. Karydas, C. E. Teunissen, J. H. Kramer, L. T. Grinberg, W. W. Seeley, H. Rosen, B. F. Boeve, B. L. Miller, G. D. Rabinovici, J. L. Dage, J. C. Rojas and A. L. Boxer (2020). "Diagnostic value of plasma phosphorylated tau181 in Alzheimer's disease and frontotemporal lobar degeneration." Nat Med **26**(3): 387-397.

Tournier, J.-D., R. Smith, D. Raffelt, R. Tabbara, T. Dhollander, M. Pietsch, D. Christiaens, B. Jeurissen, C.-H. Yeh and A. Connelly (2019). "MRtrix3: A fast, flexible and open software framework for medical image processing and visualisation." Neuroimage **202**: 116137.

van Dyck, C. H., C. J. Swanson, P. Aisen, R. J. Bateman, C. Chen, M. Gee, M. Kanekiyo, D. Li, L. Reyderman, S. Cohen, L. Froelich, S. Katayama, M. Sabbagh, B. Vellas, D. Watson, S. Dhadda, M. Irizarry, L. D. Kramer and T. Iwatsubo (2022). "Lecanemab in Early Alzheimer's Disease." New England Journal of Medicine **388**(1): 9-21.

Wimo, A., M. Guerchet, G. C. Ali, Y. T. Wu, A. M. Prina, B. Winblad, L. Jonsson, Z. Liu and M. Prince (2017). "The worldwide costs of dementia 2015 and comparisons with 2010." Alzheimers Dement **13**(1): 1-7.

### **Disclaimer**

*This project has received funding from the European Union's Horizon Europe research and innovation programme under grant agreement No 101058516. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or other granting authorities. Neither the European Union nor other granting authorities can be held responsible for them.*