Neuroscience 584 (2025) 127–137

Contents lists available at ScienceDirect

Neuroscience

journal homepage: www.elsevier.com/locate/nsc

Perspective

An integrated computational approach for diversity-sensitive personalized medicine

Carlos Coronel-Oliveros [a,b,c,d,1,*], Marilyn Gatica [e,f,1], Rubén Herzog [a,g,1], Matteo Neri [h,1]

[a] Latin American Brain Health Institute (BrainLat), Universidad Adolfo Ibañez, Santiago de Chile, Chile
[b] Trinity College Dublin, The University of Dublin, Dublin, Ireland
[c] Global Brain Health Institute (GBHI), University of California, San Francisco, United States
[d] Trinity College Dublin, Dublin, Ireland
[e] Network Science Institute, Northeastern University London, London E1W LP, United Kingdom
[f] Precision Imaging, School of Medicine, University of Nottingham, United Kingdom
[g] Instituto de Física Interdisciplinar y Sistemas Complejos (IFISC, UIB-CSIC), Campus UIB, Palma de Mallorca, Spain
[h] Institut de Neurosciences de la Timone, Aix-Marseille Université, UMR 7289 CNRS, Marseille, France

ARTICLE INFO

Keywords
Whole-brain modeling
Personalized medicine
High-order interactions
Brain health
Dementia
Diversity
Global south

ABSTRACT

Diversity in biological, social, and environmental factors plays a central role in shaping brain health and disease. Distinct brain disorders frequently exhibit overlapping clinical phenotypes, despite arising from heterogeneous biological and contextual mechanisms. This convergence challenges conventional, population-averaged approaches, which often fail to capture interindividual variability and lead to limited reproducibility, weak translational potential, and inadequate tools for individual-level characterization. To address these gaps, we propose an integrative computational approach that unites normative models of brain aging ("brain clocks"), high-order interactions, and whole-brain modeling. Brain clocks estimate individualized brain health scores by comparing observed brain features to normative age-based trajectories. Brain high-order interactions capture functional dependencies beyond pairwise connectivity, offering sensitive biomarkers that reflect system-level diversity in aging and neurodegeneration. Whole-brain modeling uses theory-based simulations of individual brain dynamics, supporting the inference of latent mechanisms and the evaluation of targeted perturbations *in silico*. Together, they form a synergistic approach: normative models provide personalized baselines, high-order interactions enhance sensitivity to complex alterations, and whole-brain simulations enable causal insight and guide potential interventions. By embedding inter-individual variability and contextual diversity into each computational layer, this framework moves the field toward precision neuroscience, where assessment, understanding, and treatment are tailored to the individuals' unique biological and social profiles.

Introduction

Diverse genetic backgrounds and socio-environmental exposomes, spanning income inequality, chronic stress, nutritional deficits, and exposure to violence, shape brain development and aging worldwide (Legaz et al., 2024; Baez et al., 2024; Santamaria-Garcia et al., 2023). This influence is particularly pronounced in the Global South, where health systems are under-resourced and research participation remains low (Parra et al., 2018; Baez et al., 2023). These regions are characterized by high levels of genetic diversity and distinct social and environmental exposomes (McGlinchey et al., 2024; Baez et al., 2023), that are known to impact brain development and aging (Legaz et al., 2024; Baez et al., 2024; Santamaria-Garcia et al., 2023). Neuropsychiatric and other brain disorders are major contributors to global disability and disease burden, particularly in aging populations (Santamaria-Garcia et al., 2023; Ibanez et al., 2024b). Among brain disorders, dementias alone already afflict over 55 million people globally, with projections surpassing 139 million by 2050, and impose an even greater burden in low- and middle-income regions, worsening disparities in care and outcomes. Existing frameworks, however, lack integrative,

* Corresponding author at: Latin American Brain Health Institute (BrainLat), Universidad Adolfo Ibañez, Santiago de Chile, Chile.
E-mail address: carlos.coronel@gbhi.org (C. Coronel-Oliveros).
[1] These authors contributed equally.

https://doi.org/10.1016/j.neuroscience.2025.08.019
Received 31 May 2025; Accepted 12 August 2025
Available online 14 August 2025

mechanistic insight, yielding results that are often irreproducible and poorly generalize across populations (Marek et al., 2022; Greene et al., 2022). In response, integrative, multimodal computational approaches offer a promising route: by combining advanced analysis of multimodal large-scale neuroimaging data with statistical and biophysical modelling, such methods can more faithfully characterize healthy aging trajectories, reveal context-specific deviations, and provide underlying biological mechanisms (Marek and Laumann, 2024; Lewandowsky and Oberauer, 2020).

There are significant barriers to implementing computational approaches in personalized medicine. Brain-derived data are often noisy, short in duration, and collected using heterogeneous protocols, limiting reproducibility and generalizability (Fan et al., 2014; Fröhlich et al., 2018). These issues are especially pronounced in under-resourced regions, where access to advanced equipment and standardized methods is limited (Yusuf et al., 2014; Archibong et al., 2025). However, beyond data limitations, meaningful clinical applications require frameworks that capture population-specific variability. Indeed, normative models, used to identify deviations from typical brain development or aging (Verdi et al., 2021), often fail to generalize when tested in diverse or underrepresented populations (Greene et al., 2022). Their lack of sensitivity to biological and environmental factors limits their application in global health. Computational neuroscience offers powerful tools to address these gaps. Advanced tools from network science, dynamical systems, information theory, machine learning, and modeling techniques can identify population-sensitive biomarkers and elucidate underlying mechanisms of brain dysfunction (Baez et al., 2024; Hernandez et al., 2024; Moguilner et al., 2024b; Santamaria-Garcia et al., 2023; Moguilner et al., 2021). These approaches not only enable the detection of disease-relevant deviations but also provide a window into the mechanistic processes shaped by genetics and the exposome (Moguilner et al., 2024b; Sanz Perl et al., 2023; Coronel-Oliveros et al., 2024; Stefanovski et al., 2019; Ranasinghe et al., 2022), offering an integrative approach that can account for diverse populations. These methods can be remotely deployed and scaled across cohorts, supporting cost-efficient, personalized, context-sensitive brain health modeling.

Here, we outline an integrated computational approach to improve brain health research across diverse populations. This proposal includes: (i) brain higher-order interactions (HOI) (Rosas et al., 2019; Herzog et al., 2022; Gatica et al., 2022; Gatica et al., 2021; Battiston et al., 2021), which capture complex multivariate dependencies in neural systems beyond pairwise functional connectivity; (ii) brain clocks, which operationalize normative brain aging and estimate deviations at the individual level (Moguilner et al., 2024a; Tian et al., 2023); and (iii) biophysical whole-brain models (WBM) (Coronel-Oliveros et al., 2024; Lynn and Bassett, 2019; Deco and Kringelbach, 2014), which test possible mechanisms underlying brain dynamics. By leveraging these complementary approaches, we propose a methodological roadmap to identify context-sensitive markers of brain health, aging, and disease, and to inform mechanistic brain function models responsive to population diversity. This synergy may lay the groundwork for a more precision-oriented neuroscience, with broad implications for personalized medicine.

Disentangling brain complexity through higher-order interactions

Phenomena such as brain aging and dementia involve a complex interplay of factors and are rarely due to dysfunction within isolated brain regions (van den Heuvel and Sporns, 2019; Damoiseaux, 2017; Betzel et al., 2014; Andrews-Hanna et al., 2007). Over the past two decades, research has shifted from focusing on individual structures to integrative approaches that examine the architecture of interactions among brain regions and neurons (Barabási, 2012). For the computation of BAG, for instance, it is often employed the functional connectivity, i.e. the connectivity between couples of brain regions is estimated as the correlation between their activities. The study of the brain as a network has improved our ability to distinguish between cognitive and pathological states and to identify the features of network organization that support specific cognitive functions or contribute to disease (Greicius, 2008). However, traditionally, these strategies focused mainly on the study of pairwise interactions, such as synapses between two neurons or correlation between two brain areas. While pairwise interactions remain central to studying brain dynamics, growing evidence supports that HOI, involving three or more neurons or brain regions simultaneously, offers deeper insights (Neri et al., 2025; Moguilner et al., 2024a; Gatica et al., 2022).

HOI can be characterized from different angles. The two main approaches are based on topological data analysis and on information theory, respectively (Fig. 1**A**) (Pope et al., 2025; Santoro et al., 2023; Santoro et al., 2024; Patania et al., 2017). Topological data analysis provides a framework to explore the higher-order architecture of brain data by identifying geometrical shapes and patterns of interdependencies with specific mathematical properties of interest (Patania et al., 2017). One widely used tool in topological data analysis is persistent homology, which focuses on topological features like cycles (e.g., recurring pathways of functional connectivity) or voids (gaps in network structure). This allows researchers to detect robust, multiscale features that traditional pairwise analyses often overlook. Insights from persistent homology can be used to build representations like the homological scaffold, that is, a network where the strength of each connection reflects its involvement in high-order topological structures, rather than just direct correlations between regions (Wasserman, 2018; Giusti et al., 2016; Zomorodian and Carlsson, 2004).

Persistent homology has been applied to investigate a broad range of cognitive and pathological conditions (Wang et al., 2023; Zhang et al., 2022). The study of specific topological features, such as one-dimensional cycles, which represent loops of interconnected brain regions, has garnered particular interest in neuroscience (Neri et al., 2024). They enable the characterization and prediction of functional alterations associated with psychiatric and neurobiological conditions such as schizophrenia (Stolz et al., 2021), epilepsy (Wang et al., 2023), attention-deficit/hyperactivity disorder and autism spectrum disorder (Lee et al., 2011), as well as to describe structural networks in healthy individuals (Sizemore et al., 2018; Petri et al., 2014). Further, persistent homology showed greater sensitivity in characterizing altered states of consciousness than the traditional pairwise approaches (Petri et al., 2014). Finally, recent research has begun to explore the dynamical properties of homological scaffolds, demonstrating that they can improve subject identifiability beyond pairwise approaches, highlighting their potential relevance for personalized medicine (Santoro et al., 2024).

On the side of information theory, HOI are captured via measuring the strength and quality of the statistical interaction (i.e., information sharing modes) among groups of brain regions from their activity recordings (e.g., fMRI or EEG) (Rosas et al., 2019). Moreover, different modes of shared information can be distinguished, specifically, redundancy (information shared across the group of variables) and synergy (information available only when considering the joint state of the whole group of variables) (Williams and Beer, 2010). Multiple metrics and computational pipelines have been introduced to quantify redundancy and synergy (Luppi et al., 2024; Neri et al., 2024; Timme et al., 2011), and recent work introduced time-resolved extensions (Pope et al., 2025; Luppi et al., 2022b), allowing for their temporal tracking and revealing dynamic changes in brain coordination that static analyses may miss.

Information theory-based HOI have been largely used to characterize development and lifespan changes in the brain of healthy populations, characterizing these phenomena in terms of synergy and redundancy. For example, in infants, a recent study identified a developmental trajectory in brain networks characterized by a shift from redundancy- to synergy-dominated neural interactions (Varley et al., 2025), modulated

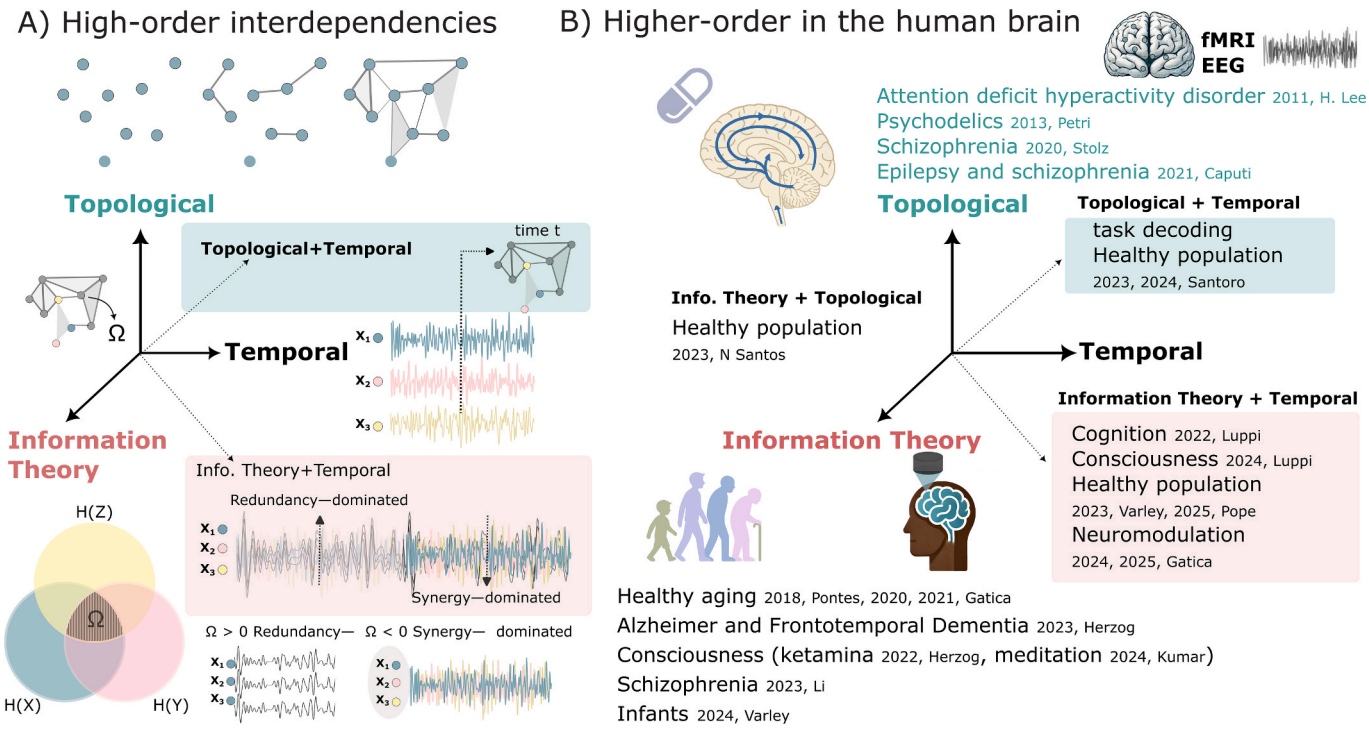

Fig. 1. Topological, information-theoretic, and temporal representation of high-order interdependencies. The topological and high-order axes represent distinct analytical perspectives, while the third axis captures their time-resolved dynamics. The intersections between these axes illustrate the integrated interpretation. **(A)** Conceptual overview of the three representational domains. **(B)** Brain-related applications in fMRI or EEG data of healthy individuals and various neurological conditions (e.g., aging, altered consciousness, Alzheimer's disease) across the three axes.

by environmental enrichment, particularly through the mother-infant connection. Across the lifespan, healthy aging is characterized by increased redundancy and loss of network/brain specialization (Camino-Pontes et al., 2018; Gatica et al., 2021). In neurodegeneration, HOI have been used to provide an accurate multimodal (EEG and fMRI) characterization of two forms of dementia: frontotemporal dementia and Alzheimer's disease (Herzog et al., 2022). On both modalities, dementia was associated with both high-order hyper and hypo-connectivity, but dominated by the former, consistent with pairwise-based analysis pointing towards dysconnectivity in dementia (van den Heuvel and Sporns, 2019). Moreover, HOI revealed specific patterns for different dementia subtypes, providing higher sensitivity compared to classical pairwise analyses (Herzog et al., 2022).

Finally, HOI can be employed to characterize the effects of non-invasive neuromodulation. For example, HOI have been used to assess the effects of low-intensity transcranial ultrasound stimulation, an emerging technique able to target cortical and deep brain structures, on brain dynamics (Darmani et al., 2022). Although the effects of neuromodulation remain unknown, HOI has proven effective in detecting stimulation-induced perturbations that extend beyond the targeted regions through functional networks in both macaques (Gatica et al., 2024) and humans (Gatica et al., 2025). These effects are target-specific and point to the potential of HOI for individualized assessment, moving beyond pairwise group-level analyses to enhance the precision and clinical relevance of neuromodulation at a single subject level. Encouragingly, public perception of such non-invasive approaches is generally positive (Atkinson-Clement et al., 2025), supporting their future clinical adoption.

Altogether, HOI provides a novel dimension for analyzing brain functional and structural data, enabling a more refined characterization of individual subjects as well as inter-group differences across various cognitive states and health conditions. Recent literature has emphasized the potential of HOI to enhance our ability to interpret complex brain data (Fig. 1**B**). In this context, HOI can be integrated with brain age prediction models, such as brain clocks, to improve the assessment of BAG (Moguilner et al., 2024a). Furthermore, the study of HOI, if combined with WBM, offers a powerful framework for exploring the effects of specific mechanisms at multiple interaction levels.

Diversity-sensitive brain clocks as normative models of brain aging

Brain clocks are computational models that estimate an individual's brain age from neuroimaging data, providing a normative score of brain health (Verdi et al., 2021; Moguilner et al., 2024a; Tian et al., 2023) (Fig. 2). Brain clocks start using machine learning or deep learning algorithms, such as support vector regression, Gaussian processes, or graph-based neural networks, trained on large functional magnetic resonance imaging (fMRI), electroencephalography (EEG), or MRI datasets to predict chronological age (Baecker et al., 2021a; Alber et al., 2019; Al Zoubi et al., 2018) (Fig. 2**A**). These models typically rely on preprocessed features like connectivity matrices or HOI derived from parcellated time series (Fig. 2**B**). After hyperparameter tuning and cross-validation, they can be used to predict age from brain-derived data. These models yield a brain age prediction (Baecker et al., 2021b), with the brain age gap (BAG) calculated as the difference between predicted and actual age (Moguilner et al., 2024a; Tian et al., 2023) (Fig. 2**C**).

The key output of these models is the BAG (Moguilner et al., 2024a; Smith et al., 2019; Tian et al., 2023). A positive BAG indicates accelerated brain aging, while a negative BAG reflects delayed aging relative to the normative reference (Moguilner et al., 2024a; Smith et al., 2019; Tian et al., 2023). These individualized scores allow for quantifying deviations from expected brain aging trajectories and have emerged as useful biomarkers for assessing brain health across diverse populations (Moguilner et al., 2024a). Because brain clocks are grounded in normative modeling, they support comparative analyses between individuals and groups, offering insight into how genetic, clinical, and environmental factors shape brain aging across the lifespan (Tian et al.,

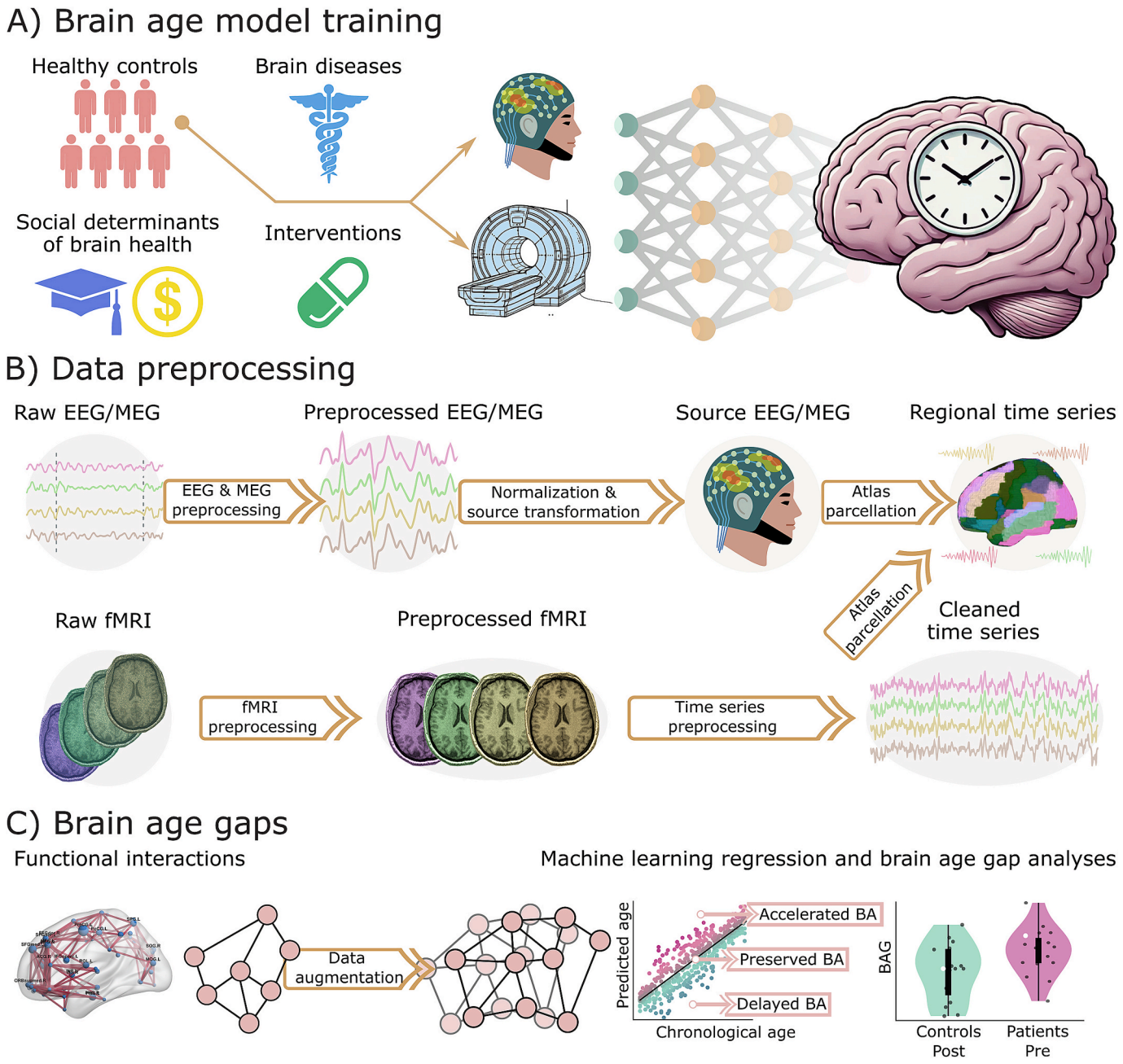

Fig. 2. Functional brain clocks' architecture. (A) Brain age models are trained using neuroimaging data (e.g., EEG, MEG, fMRI) from large cohorts of healthy individuals. The trained models can predict the brain age of patients with brain-related conditions and individuals exposed to varying social determinants or interventions. **(B)** Data preprocessing involves signal cleaning, normalization, and transformation into a common brain space (e.g., source projection and anatomical parcellation) to extract regional time series. These features capture functional dynamics across brain networks. Non-functional data, for example, gray matter volume and white matter hyperintensities, can be used to train brain clocks or can be mixed with functional data as well. **(C)** Functional connectivity matrices or graph representations are derived from the time series and used to train machine learning models (e.g., support vector machines, graph neural networks) to predict brain age. The difference between predicted and chronological age, known as the brain age gap (BAG), serves as an individualized index of brain aging. Positive BAG suggest accelerated brain aging, while negative BAG indicate delayed or preserved aging trajectories.

2023; Verdi et al., 2021). When paired with multimodal neuroimaging and electrophysiological data, brain clocks represent a scalable, simple, and practical framework for studying brain health in global settings, including basic and clinical research.

Brain clocks have been applied to characterize brain aging in the context of neurological and psychiatric disorders (Tian et al., 2023; Cole et al., 2017; Moguilner et al., 2024a; Baecker et al., 2021b; Coronel-Oliveros et al., 2025b). They have shown consistent evidence of accelerated brain aging across conditions such as schizophrenia, major depression, epilepsy, and dementia-related syndromes (Tian et al., 2023; Cole et al., 2017; Baecker et al., 2021b; Coronel-Oliveros et al., 2025b). A possible way to extend brain clocks is by incorporating functional HOI into models, improving their sensitivity to subtle and distributed alterations in brain dynamics (Moguilner et al., 2024a). This has proven especially valuable in characterizing aging deviations across the dementia continuum, including mild cognitive impairment, Alzheimer's disease, and frontotemporal dementia, where increased BAG were observed, consistent with disease progression (Moguilner et al., 2024a). These models based on HOI have also revealed marked differences between populations from the Global North and South, detecting

accelerated brain aging in Latinos versus the Global North participants, which was modulated by biological sex, even after controlling for technical and demographic confounds (Moguilner et al., 2024a; Coronel-Oliveros et al., 2025b). Importantly, the robustness of these brain clock models has been supported by harmonization pipelines (Prado et al., 2023b, Prado et al., 2023a; Prado et al., 2022; Parra-Rodriguez et al., 2022) that reduce variability arising from different recording devices, acquisition protocols, and signal quality (Prado et al., 2023b; Prado et al., 2023a; Prado et al., 2022; Parra-Rodriguez et al., 2022).

Beyond disease classification, brain clocks can be applied to assess the influence of lifestyle and interventions on brain aging (Tian et al., 2023; Matziorinis et al., 2023, Rogenmoser et al., 2018, Baecker et al., 2021b, Le et al., 2018, Richard et al., 2020, Pardoe et al., 2017). BAG have been linked to modifiable risk factors such as alcohol consumption, physical activity, and dietary patterns (Tian et al., 2023). For example, individuals engaged in creative activities, such as playing musical instruments, dancing, visual arts, or strategy-based video games, exhibit delayed brain aging across several domains (Coronel-Oliveros et al., 2025a), through mechanisms related to neural plasticity (Sampaio-Baptista and Johansen-Berg, 2017; Fields, 2015; Coronel-Oliveros et al., 2024; Kowalczyk et al., 2018). Furthermore, using a pre/post-learning design, brain clocks can detect short-term brain changes in response to non-pharmacological interventions (Coronel-Oliveros et al., 2025a), offering a framework to monitor the direct impact of experiential and cognitive stimulation on brain health. In individuals with schizophrenia, brain clocks have also been used to assess the effects of physical training, revealing delayed brain aging following intervention, with BAG reductions correlating with improvements in clinical symptoms (Yilmaz et al., 2025). In this way, brain clocks can provide robust and clear metrics about the effects of modifiable factors and pharmacological therapies on brain health, contributing to delivering more precise information about preventive and tailored strategies for public health policies.

Emerging directions in brain clock research aim to bridge these models with other biological clocks, such as epigenetic, metabolomic, and organ-specific clocks (Jia et al., 2024; Argentieri et al., 2025; Tian et al., 2023) to build more integrative assessments of biological aging. The integration of brain clock models with HOI biomarkers holds significant potential for advancing our ability to characterize the neural mechanisms underlying aging (Moguilner et al., 2024a; Gatica et al., 2022; Gatica et al., 2021). This approach may facilitate earlier detection and enable more personalized monitoring of individuals at elevated risk for age-related cognitive decline. Moreover, advances in low-cost and scalable technologies, such as portable EEG systems, enable the deployment of brain clock models in resource-limited settings, expanding their accessibility, especially in low and middle-income countries. These portable devices, integrated with brain clocks, can lead to the development of real-life health monitoring tools. Another promising avenue is the development of region or network-specific brain clocks that track aging within distinct functional or structural brain systems (Leake, 2024). These mesoscopic-level models can reveal disease-specific patterns of accelerated aging and may improve the specificity and interpretability of brain health assessments across neurological and psychiatric conditions.

Whole-brain modeling as a clinical test bench for interventions

Statistical and machine learning approaches offer powerful predictive capabilities but remain as “black boxes”, limiting mechanistic insights into brain dynamics and function. WBM provide a complementary alternative and enable a mechanistic understanding of brain health, disorders, accelerated aging, and population-level diversity (Deco and Kringelbach, 2014). They provide a principled approach to link brain structure and function, and have recently been called “an essential tool for understanding brain dynamics” (Patow et al., 2024). To simulate brain activity, WBM leverage multimodal brain data by incorporating neuroimaging and biophysical priors, such as brain anatomical (structural) connectivity, gene and protein expression maps, or atrophy maps. The typical WBM framework involves using the model to reproduce some empirical features of brain dynamics by optimizing free parameters with a biological interpretation (Patow et al., 2024, Deco and Kringelbach, 2014). In this way, it is possible to provide interpretability and a causal framework where empirical patterns of healthy and pathological brain dynamics can be linked to specific neural mechanisms. The goal would be to develop the so-called ‘digital twins’, specifically for the brain (i.e. personalized virtual brains) (Wang et al., 2024, Laubenbacher et al., 2024). Digital brain twins are not replicas of the brain *per se*, but models able to reproduce brain dynamics and allow testing mechanistic hypotheses can be tested *in silico* (Wang et al., 2024). They provide a means to identify, beforehand, subject-specific vulnerabilities and potential treatment targets, which can then be tested in real experimental settings.

WBM are typically built by integrating three key components (Fig. 3**A**) (Lynn and Bassett, 2019, Deco and Kringelbach, 2014): (i) empirical priors, (ii) local dynamics, and (iii) an objective function. First, empirical priors serve as the anatomical and physiological scaffold of the model. These include subject-specific or population-derived data such as structural connectivity (from diffusion MRI), functional parcellations, gene expression gradients, neurotransmitter receptor densities (obtained from positron emission tomography; PET), or disease-specific atrophy maps (Deco et al., 2018, Moguilner et al., 2024c, Luppi et al., 2022a, Coronel-Oliveros et al., 2023, Shen et al., 2012). Second, local dynamics are defined by mathematical models that generate the activity of each brain region. These may range from pure phenomenological models (Ponce-Alvarez and Deco, 2024, Cabral et al., 2014, Sampaio Filho et al., 2024) to biophysical models (Deco et al., 2014, Jansen and Rit, 1995), covering the whole range of neural activity from the neuron level to large-scale brain dynamics (Lynn and Bassett, 2019). Finally, the model is calibrated to match empirical brain activity by tuning a set of biologically meaningful parameters, such as global coupling, local excitation/inhibition balance, or average firing rates across regions. This process aims to reproduce key brain features, including functional connectivity, power spectra, and dynamic patterns. To guide this fitting, an objective function is used, typically based on similarity measures, for example, the correlation between empirical and simulated functional connectivity.

Crucially, personalized models can act as mechanistic classifiers (Fig. 3**B**), offering insights that go beyond symptom-based categorization. By projecting empirical data onto a constrained space of neurobiological mechanisms, they enable patient stratification based on physiological parameters such as regional excitability, inhibition, or disrupted anatomical connectivity. For example, when informed by empirical priors, these models can capture how neurodegenerative processes interact with biological sex, disease progression, and regional vulnerability (Moguilner et al., 2024c). Simulations based on resting-state EEG and fMRI have revealed regionally imbalanced excitation-inhibition dynamics in dementia, with modulatory effects linked to sex and sociodemographic context, underscoring how structural inequalities may shape brain health trajectories (Moguilner et al., 2024c, Coronel-Oliveros et al., 2025b (manuscript accepted), Coronel-Oliveros et al., 2025a, Coronel-Oliveros et al., 2025b). Dynamical models have also been used to simulate transitions between pathological and healthy brain states, identifying control targets that could guide neuromodulation (Sanz Perl et al., 2023). These frameworks are being extended to simulate pharmacological interventions *in silico*, integrating PET-based receptor maps to explore how neuromodulatory systems can move the dynamics in patients with disorders of consciousness closer to healthy brain dynamics (Mindlin et al., 2024). Together, these approaches illustrate how WBM can bridge neural mechanisms with contextual diversity, supporting personalized assessments and intervention strategies (Fig. 3**C**).

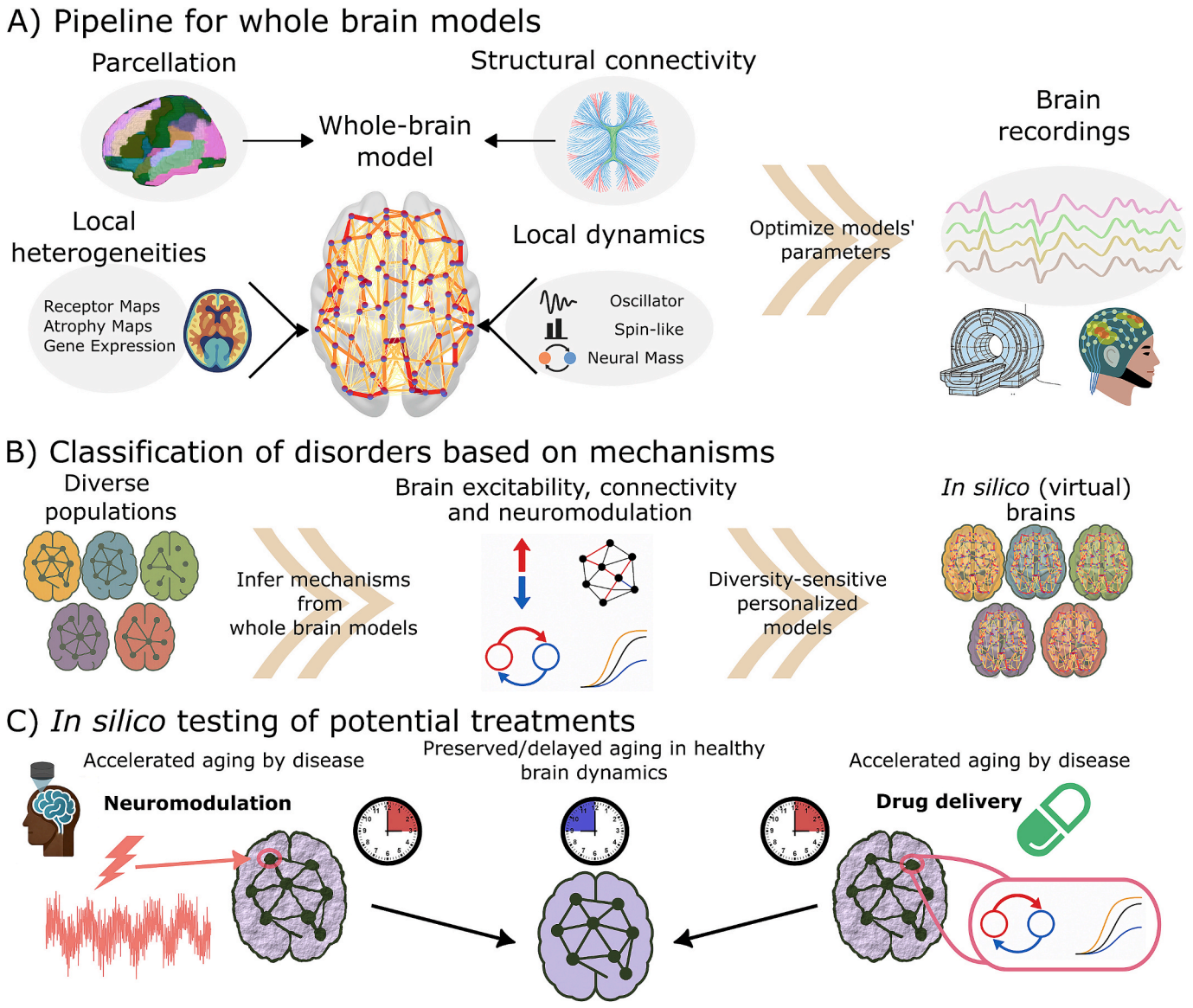

Fig. 3. A framework for diversity-sensitive whole-brain modelling. (A) The general pipeline for building whole brain models. Note that the local heterogeneities and the structural connectivity matrix are empirical priors, while the local dynamics depends on the level of realisms to be explained. **(B)** Once whole-brain models are optimized to individual subjects or specific population, the inferred mechanisms can be used to classify different disorders. **(C)** Using the diversity-sensitive whole-brain models, specific treatments can be evaluated "*in silico*", accelerating the discovery of personalized treatments.

Recent works have included HOI in whole-brain modelling pipelines. These models have successfully been used to characterize the effects of non-invasive neuromodulation (Gatica et al., 2025), and the alterations of brain dynamics in healthy aging (Gatica et al., 2021). In this way, WBM revealed that, in aging, the increase in brain redundancy (see previous section) can be explained by a process of connectome degeneration (Gatica et al., 2022). Similar mechanisms have been proposed in neurodegeneration (Coronel-Oliveros et al., 2024; Amato et al., 2024). WBM have been used to reproduce HOI in dementia (Coronel-Oliveros et al., 2024; Arbabyazd et al., 2023). These models suggest that brain dynamics in Alzheimer's disease and frontotemporal dementia emerge from a combination of two different mechanisms. One mechanism consisted of connectome degeneration, that is, the weakening of white matter tracts. The other one corresponds to neural hypoexcitability, producing a frustrated or "viscous" brain dynamics. As a limitation, works in the field of WMB reproduce high-order behavior without high-order mechanisms (Robiglio et al., 2025, Rosas et al., 2022). A promising direction is to embed these mechanisms in WBM, e.g., by reducing the pairwise structural connectivity matrix to a small set of high-order structural connections.

Finally, brain disorders often present with overlapping clinical phenotypes despite arising from diverse biological, social, and cultural influences (Verdi et al., 2021). This phenotypic convergence shows the limitations of one-size-fits-all explanations (Ibanez et al., 2024c, Ibanez et al., 2024a). Rather than searching for universal mechanisms, it becomes necessary to account for the multiple, interacting pathways that can give rise to similar outcomes. This recognition points out the need for individualized frameworks that can identify person-specific targets and disease trajectories. WBM may tackle this challenge by offering a computational platform that integrates multimodal data to simulate brain activity at the individual level. By grounding in mechanistic principles and adapting to diverse priors, WBM enable hypothesis testing, inference of hidden parameters, and virtual interventions tailored to each participant's brain (Wang et al., 2024, Coronel-Oliveros et al., 2024, Deco et al., 2019, Sanz Perl et al., 2023), moving neuroscience toward a more precise, context-sensitive understanding of brain health and disease.

A synergistic computational proposal for personalized medicine

Diversity, reflected in genetics, education, socioeconomic status, and environmental exposures, shapes brain health across the lifespan. Instead of filtering it out, we need approaches that remain sensitive to such variability without losing meaningfulness. By combining empirical characterization with novel computational architectures, we can move beyond population averages and identify individual-level deviations that reflect both biological and contextual factors. This allows us to address diversity not as a limitation, but as a necessary dimension of precision neuroscience.

Our synergistic proposal consisted of combining all the methods presented here into a diversity-sensitive integrative computational approach. HOI provide a powerful way to detect subtle and distributed alterations in brain networks, offering sensitive biomarkers even for preclinical manifestations of brain diseases (Haghayegh et al., 2025), though this requires further exploration and validation. This sensitivity makes HOI valuable for understanding dementia progression, tracking healthy aging, and assessing neuromodulatory interventions (Gatica et al., 2025). By integrating HOI into normative modeling frameworks, such as brain clocks, we can derive biologically grounded, network-specific BAG that quantify deviations from healthy aging at the individual level. Then, WBM can take these deviations as input, simulating the underlying biophysical dynamics and inferring causal mechanisms to better classify the different trajectories associated with individual healthy or pathological ageing. Finally, these models enable "*in silico*" testing of which perturbations (stimulation targets or pharmacological manipulations) most effectively reduce BAG. This synergy transforms descriptive biomarkers into actionable mechanisms, creating a test-bench for identifying potential therapeutic interventions. This synergistic loop of HOI to clocks, clocks to WBM, WBM to interventions, constitutes a computational approach with the full potential of transforming brain health and personalized medicine (Fig. 4).

Limitations and future work

To conclude we acknowledge few critical points of the proposed pipeline that might limit the impact of the proposed pipeline. First, a key technical limitation in BAG analyses relies on age bias; the BAG can be biased by age-related regression to the mean (Beheshti et al., 2019, Treder et al., 2021). To solve this issue, one can employ correction methods like residualization or age-matched designs, though these may artificially inflate model performance if not applied cautiously (Butler et al., 2021). Second, BAG might capture, beyond disease, the accumulative burden of the environmental, socioeconomical and political exposomes (Hernandez et al., 2025, Moguilner et al., 2024a), fact that may constitute a challenge when comparing accelerated aging across different generations, countries and cultures.

A key limitation in investigating HOI through information theory and topological data analysis lies in the substantial computational cost,

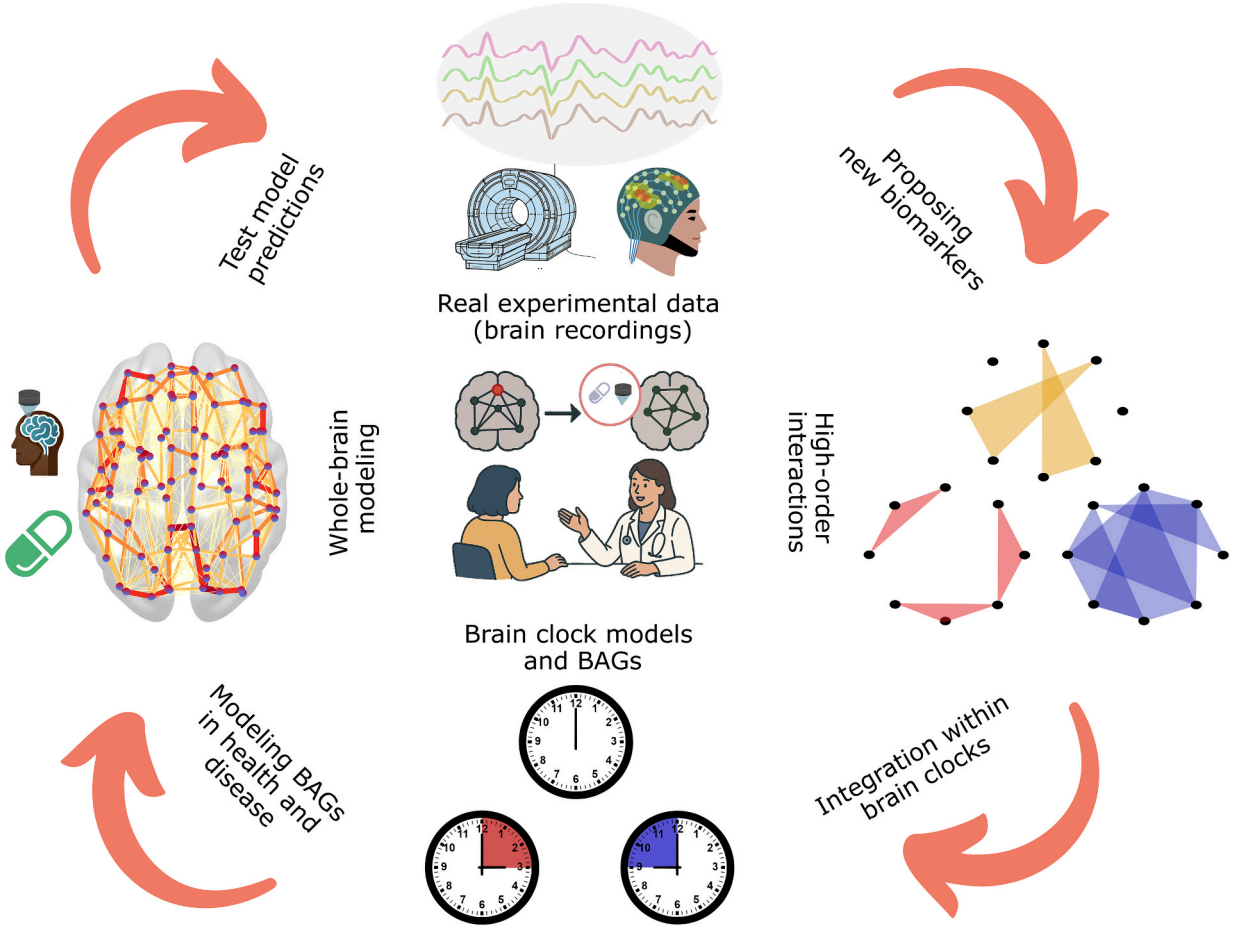

Fig. 4. A synergistic computational framework for diversity sensitive personalized medicine. The figure illustrates a synergistic loop in which three complementary computational approaches (brain clocks, WBM, and HOI) synergize to enable a personalized characterization of brain health and disease, uncover underlying mechanisms, and inform targeted therapeutic interventions. Within this framework, brain data are first characterized using HOI analysis, providing rich, multi-scale descriptors of brain function. These descriptors can improve the estimation of biological brain age via brain clock models and the derivation of brain age gaps. Subsequently, whole-brain models provide mechanistic insights into how interventions, including pharmacological treatments, may positively influence brain health. Hypotheses generated through WBM are then validated experimentally, requiring new data collection, closing the cycle.

which increases exponentially with the order of interactions considered. This challenge also extends to WBM, where exploring the parameter space becomes increasingly demanding as the number of parameters grows. While these computational demands must be carefully accounted for when applying our proposed framework, recent advances in algorithmic and computational tools have significantly improved our capacity to manage such complexity, paving the way for future developments (Neri et al., 2024, Herzog et al., 2024b, Belloli et al., 2025).

Another limitation concerns data availability and quality. Although our pipeline is designed to operate with currently available brain and behavioral datasets, integrating them into a closed-loop fashion without requiring major new infrastructure, its performance may be hindered by missing or low-quality data. This concern is particularly relevant for applications in low- and middle-income countries. Therefore, a critical direction for future work involves the development of novel data collection strategies and supporting infrastructures aimed at improving data quality and accessibility in these contexts. For these computational advances to have a real-world impact, they must be translated into tools suitable for clinical and community settings. Emerging technologies such as portable EEG (Barbey et al., 2022), low-field MRI (Arnold et al., 2023), and wearable sensors (Byrom et al., 2018) offer unprecedented access to brain data outside of research laboratories. With these acquisitions setups combined with robust computational methods, even low-cost signals can be transformed into powerful indicators of individual brain health. For instance, EEG-based HOI has been proven to be sensitive enough to track the brain and subjective alterations under the effect of pharmacological interventions (Herzog et al., 2024a). This approach is promising for under-resourced settings, where access to high-end neuroimaging is limited.

Conclusion and final remarks

In summary, we have reviewed the core concepts underlying three distinct lines of research and proposed a strategy that integrates them into a unified pipeline. This approach aims to support personalized models and precision medicine. By combining our proposal with innovative data collection strategies, we envision the development of a closed-loop framework in which data acquisition, model-based inference, and adaptive intervention are tightly integrated.

Software

All figures were generated using Python 3.12.3, MATLAB R2023a, and AI-assisted design tools. We employed the Matplotlib 3.8.4 and Seaborn 0.13.2 libraries. Brains with connections were created in using BrainNet Viewer (Xia et al., 2013). Figures were further refined using Inkscape.

CRediT authorship contribution statement

Carlos Coronel-Oliveros: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Marilyn Gatica:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis. **Rubén Herzog:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis. **Matteo Neri:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Conceptualization.

Acknowledgments

CCO is supported by a postdoctoral grant from BrainLat. MG acknowledges the funding support of the Institute for Advanced Study (IAS, Amsterdam), which provided not only financial support but also a stimulating intellectual environment that contributed significantly to the development of this work. MN has received funding from the French government under the 'France 2030' investment plan managed by the French National Research Agency (Agence Nationale de la Recherche; reference: ANR-16- CONV000X/ANR-17-EURE- 0029) and from the Excellence Initiative of Aix-Marseille University—A*MIDEX (AMX-19-IET- 004). RH was supported by the Ramón y Cajal Fellowship (RYC2022-035106-I) from FSE/Agencia Estatal de Investigación (AEI), Spanish Ministry of Science and Innovation, and the María de Maeztu Program for units of Excellence in R&D, grant CEX2021-001164-M/10.13039/501100011033.

References

Al Zoubi, O., Ki Wong, C., Kuplicki, R.T., Yeh, H.-W., Mayeli, A., Refai, H., Paulus, M., Bodurka, J., 2018. Predicting age from brain EEG signals—a machine learning approach. Front. Aging Neurosci. 10.

Alber, M., Buganza Tepole, A., Cannon, W.R., De, S., Dura-Bernal, S., Garikipati, K., Karniadakis, G., Lytton, W.W., Perdikaris, P., Petzold, L., Kuhl, E., 2019. Integrating machine learning and multiscale modeling—perspectives, challenges, and opportunities in the biological, biomedical, and behavioral sciences. NPJ Dig. Med. 2, 115.

Amato, L.G., Vergani, A.A., Lassi, M., Fabbiani, C., Mazzeo, S., Burali, R., Nacmias, B., Sorbi, S., Mannella, R., Grippo, A., 2024. Personalized modeling of Alzheimer's disease progression estimates neurodegeneration severity from EEG recordings. Alzheim. Demen.: Diagn. Assess. Disease Monitor. 16.

Andrews-Hanna, J.R., Snyder, A.Z., Vincent, J.L., Lustig, C., Head, D., Raichle, M.E., Buckner, R.L., 2007. Disruption of large-scale brain systems in advanced aging. Neuron 56, 924–935.

Arbabyazd, L., Petkoski, S., Breakspear, M., Solodkin, A., Battaglia, D., Jirsa, V., 2023. State-switching and high-order spatiotemporal organization of dynamic functional connectivity are disrupted by Alzheimer's disease. Network Neurosci. 1–32.

Archibong, V., Samson, O., Akeem, O., Abdullahi, M., Akaninyene, I., Micheal, I.U., Gashegu, J., 2025. Promoting Neuroscience Research and Education in Limited-resource Settings: Neuroscience-in-view at the University of Rwanda.

Argentieri, M.A., Amin, N., Nevado-Holgado, A.J., Sproviero, W., Collister, J.A., Keestra, S.M., Kuilman, M.M., Ginos, B.N., Ghanbari, M., Doherty, A., 2025. Integrating the environmental and genetic architectures of aging and mortality. Nat. Med. 1–10.

Arnold, T.C., Freeman, C.W., Litt, B., Stein, J.M., 2023. Low-field MRI: clinical promise and challenges. J. Magn. Reson. Imag. 57, 25–44.

Atkinson-Clement, C., Junor, A., Kaiser, M., 2025. Neuromodulation perception by the general public. Sci. Rep. 15, 5584.

Baecker, L., Dafflon, J., da Costa, P.F., Garcia-Dias, R., Vieira, S., Scarpazza, C., Calhoun, V.D., Sato, J.R., Mechelli, A., Pinaya, W.H.L., 2021a. Brain age prediction: a comparison between machine learning models using region- and voxel-based morphometric data. Hum. Brain Mapp. 42, 2332–2346.

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

Baez, S., Alladi, S., Ibanez, A., 2023. Global South research is critical for understanding brain health, ageing and dementia. Clin. Transl. Med. 13.

Baez, S., Hernandez, H., Moguilner, S., Cuadros, J., Santamaria-Garcia, H., Medel, V., Migeot, J., Cruzat, J., Valdes-Sosa, P.A., Lopera, F., González-Hernández, A., Bonilla-Santos, J., Gonzalez-Montealegre, R.A., Aktürk, T., Legaz, A., Altschuler, F., Fittipaldi, S., Yener, G.G., Escudero, J., Babiloni, C., Lopez, S., Whelan, R., Lucas, A. A.F., Huepe, D., Soto-Añari, M., Coronel-Oliveros, C., Herrera, E., Abasolo, D., Clark, R.A., Güntekin, B., Duran-Aniotz, C., Parra, M.A., Lawlor, B., Tagliazucchi, E., Prado, P., Ibanez, A., 2024. Structural inequality and temporal brain dynamics across diverse samples. Clin. Transl. Med. 14, e70032.

Barabási, A.-L., 2012. The network takeover. Nat. Phys. 8, 14–16.

Barbey, F.M., Farina, F.R., Buick, A.R., Danyeli, L., Dyer, J.F., Islam, M.N., Krylova, M., Murphy, B., Nolan, H., Rueda-Delgado, L.M., 2022. Neuroscience from the comfort of your home: repeated, self-administered wireless dry EEG measures brain function with high fidelity. Front. Dig. Health 4, 944753.

Battiston, F., Amico, E., Barrat, A., Bianconi, G., Ferraz De Arruda, G., Franceschiello, B., Iacopini, I., Kéfi, S., Latora, V., Moreno, Y., 2021. The physics of higher-order interactions in complex systems. Nat. Phys. 17, 1093–1098.

Beheshti, I., Nugent, S., Potvin, O., Duchesne, S., 2019. Bias-adjustment in neuroimaging-based brain age frameworks: a robust scheme. NeuroImage: Clin. 24, 102063.

Belloli, L., Mediano, P., Cofré, R., Slezak, D. F., Herzog, R., 2025. THOI: An efficient and accessible library for computing higher-order interactions enhanced by batch-processing. *arXiv preprint arXiv:2501.03381*.

Betzel, R.F., Byrge, L., He, Y., Goñi, J., Zuo, X.-N., Sporns, O., 2014. Changes in structural and functional connectivity among resting-state networks across the human lifespan. Neuroimage 102, 345–357.

Butler, E.R., Chen, A., Ramadan, R., Le, T.T., Ruparel, K., Moore, T.M., Satterthwaite, T. D., Zhang, F., Shou, H., Gur, R.C., 2021. Pitfalls in Brain Age Analyses. Wiley Online Library.

Byrom, B., McCarthy, M., Schueler, P., Muehlhausen, W., 2018. Brain monitoring devices in neuroscience clinical research: the potential of remote monitoring using sensors, wearables, and mobile devices. Clin. Pharmacol. Ther. 104, 59–71.

Cabral, J., Luckhoo, H., Woolrich, M., Joensson, M., Mohseni, H., Baker, A., Kringelbach, M.L., Deco, G., 2014. Exploring mechanisms of spontaneous functional connectivity in MEG: how delayed network interactions lead to structured amplitude envelopes of band-pass filtered oscillations. Neuroimage 90, 423–435.

Camino-Pontes, B., Diez, I., Jimenez-Marin, A., Rasero, J., Erramuzpe, A., Bonifazi, P., Stramaglia, S., Swinnen, S., Cortes, J.M., 2018. Interaction information along lifespan of the resting brain dynamics reveals a major redundant role of the default mode network. Entropy 20, 742.

Cole, J.H., Annus, T., Wilson, L.R., Remtulla, R., Hong, Y.T., Fryer, T.D., Acosta-Cabronero, J., Cardenas-Blanco, A., Smith, R., Menon, D.K., 2017. Brain-predicted age in down syndrome is associated with beta amyloid deposition and cognitive decline. Neurobiol. Aging 56, 41–49.

Coronel-Oliveros, C., Gießing, C., Medel, V., Cofré, R., Orio, P., 2023. Whole-brain modeling explains the context-dependent effects of cholinergic neuromodulation. Neuroimage 265, 119782.

Coronel-Oliveros, C., Medel, V., Orellana, S., Rodiño, J., Lehue, F., Cruzat, J., Tagliazucchi, E., Brzezicka, A., Orio, P., Kowalczyk-Grębska, N., 2024a. Gaming expertise induces meso-scale brain plasticity and efficiency mechanisms as revealed by whole-brain modeling. Neuroimage 293, 120633.

Coronel-Oliveros, C., Migeot, J., Lehue, F., Amoruso, L., Kowalczyk-Grębska, N., Jakubowska, N., Mandke, K., Pereira Seabra, J., Orio, P., Campbell, D., Gonzalez-gomez, R., Prado, P., Cuadros, J., Tagliazucchi, E., Cruzat, J., Legaz, A., Medel, V., Hernández, H., Fittipaldi, S., Altschuler, F., Moguilner, S., Baez, S., Santamaría-garcía, H., González-hernández, A., Bonilla-santos, J., Güntekin, B., Babiloni, C., Abasolo, D., Di caterina, G., Yener, G.G., Escudero, J., Ochoa gómez, J.F., Soto-añari, M., Bruno, M., Valdes-sosa, P., Anghinah, R., Gonzalez-montealegre, R.A., Clark, R., García, A., Kaltwasser, L., Schürmann, M., Meier, J., Brzezicka, A., Whelan, R., Lawlor, B., Robertson, I., Bailey, C., Melloni, I., Sajnani, N., Ibáñez, A., 2025a. Creative experiences and brain clocks. Nat. Commun.

Coronel-Oliveros, C., Moguilner, S., Hernandez, H., Cruzat, J., Baez, S., Medel, V., Cuadros, J., Santamaria-Garcia, H., Valdes-Sosa, P.A., Lopera, F., Ochoa-Gómez, J.F., González-Hernández, A., Bonilla-Santos, J., Gonzalez-Montealegre, R.A., Aktürk, T., Yıldırım, E., Anghinah, R., Legaz, A., Fittipaldi, S., Yener, G.G., Escudero, J., Babiloni, C., Lopez, S., Whelan, R., Fernández, A., Huepe, D., Di Caterina, G., Soto-Añari, M., Gonzalez-Gomez, R., Herrera, E., Abasolo, D., Kilborn, K., Rubido, N., Clark, R., Herzog, R., Yerlikaya, D., Güntekin, B., Deco, G., Prado, P., Parra, M.A., Orio, P., Tagliazucchi, E., Lawlor, B., Ibañez, A., 2025b. Diversity-sensitive brain clocks linked to biophysical mechanisms in aging and dementia. Nat. Ment. Health. Accepted/In press.

Coronel-Oliveros, C., Gómez, R.G., Ranasinghe, K., Sainz-Ballesteros, A., Legaz, A., Fittipaldi, S., Cruzat, J., Herzog, R., Yener, G., Parra, M., Aguillon, D., Lopera, F., Santamaria-Garcia, H., Moguilner, S., Medel, V., Orio, P., Whelan, R., Tagliazucchi, E., Prado, P., Ibañez, A., 2024b. Viscous dynamics associated with hypoexcitation and structural disintegration in neurodegeneration via generative whole-brain modeling. Alzheimers Dement.

Damoiseaux, J.S., 2017. Effects of aging on functional and structural brain connectivity. Neuroimage 160, 32–40.

Darmani, G., Bergmann, T., Pauly, K.B., Caskey, C., de Lecea, L., Fomenko, A., Fouragnan, E., Legon, W., Murphy, K., Nandi, T., 2022. Non-invasive transcranial ultrasound stimulation for neuromodulation. Clin. Neurophysiol. 135, 51–73.

Deco, G., Cruzat, J., Cabral, J., Knudsen, G.M., Carhart-Harris, R.L., Whybrow, P.C., Logothetis, N.K., Kringelbach, M.L., 2018. Whole-brain multimodal neuroimaging model using serotonin receptor maps explains non-linear functional effects of LSD. Curr. Biol. 28, 3065–3074.e6.

Deco, G., Cruzat, J., Cabral, J., Tagliazucchi, E., Laufs, H., Logothetis, N.K., Kringelbach, M.L., 2019. Awakening: predicting external stimulation to force transitions between different brain states. Proc. Natl. Acad. Sci. 116, 18088–18097.

Deco, G., Kringelbach, Morten l., 2014. Great expectations: using whole-brain computational connectomics for understanding neuropsychiatric disorders. Neuron 84, 892–905.

Deco, G., Ponce-Alvarez, A., Hagmann, P., Romani, G.L., Mantini, D., Corbetta, M., 2014. How local excitation-inhibition ratio impacts the whole brain dynamics. J. Neurosci. 34, 7886–7898.

Fan, J., Han, F., Liu, H., 2014. Challenges of big data analysis. Natl. Sci. Rev. 1, 293–314.

Fields, R.D., 2015. A new mechanism of nervous system plasticity: activity-dependent myelination. Nat. Rev. Neurosci. 16, 756–767.

Fröhlich, H., Balling, R., Beerenwinkel, N., Kohlbacher, O., Kumar, S., Lengauer, T., Maathuis, M.H., Moreau, Y., Murphy, S.A., Przytycka, T.M., 2018. From hype to reality: data science enabling personalized medicine. BMC Med. 16, 1–15.

Gatica, M., Atkinson-Clement, C., Coronel-Oliveros, C., Alkhawashki, M., Mediano, P. A., Tagliazucchi, E., Rosas, F. E., Kaiser, M. & Petri, G., 2025. Understanding the high-order network plasticity mechanisms of ultrasound neuromodulation. *bioRxiv*, 2025.01. 11.632528.

Gatica, M., Atkinson-Clement, C., Mediano, P.A., Alkhawashki, M., Ross, J., Sallet, J., Kaiser, M., 2024. Transcranial ultrasound stimulation effect in the redundant and synergistic networks consistent across macaques. Network Neurosci. 8, 1032–1050.

Gatica, M., Cofré, R., Mediano, P.A.M., Rosas, F.E., Orio, P., Diez, I., Swinnen, S.P., Cortes, J.M., 2021. High-order interdependencies in the aging brain. Brain Connect. 11, 734–744.

Gatica, M.E., Rosas, F.A.M., Mediano, P., Diez, I., Swinnen, S.P., Orio, P., Cofré, R., Cortes, M.J., 2022. High-order functional redundancy in ageing explained via alterations in the connectome in a whole-brain model. PLoS Comput. Biol. 18, e1010431.

Giusti, C., Ghrist, R., Bassett, D.S., 2016. Two's company, three (or more) is a simplex: Algebraic-topological tools for understanding higher-order structure in neural data. J. Comput. Neurosci. 41, 1–14.

Greene, A.S., Shen, X., Noble, S., Horien, C., Hahn, C.A., Arora, J., Tokoglu, F., Spann, M. N., Carrión, C.I., Barron, D.S., Sanacora, G., Srihari, V.H., Woods, S.W., Scheinost, D., Constable, R.T., 2022. Brain–phenotype models fail for individuals who defy sample stereotypes. Nature 609, 109–118.

Greicius, m., 2008. Resting-state functional connectivity in neuropsychiatric disorders. Curr. Opin. Neurol. 21, 424–430.

Haghayegh, S., Herzog, R., Bennett, D.A., Redline, S., Yaffe, K., Stone, K.L., Ibáñez, A., Hu, K., 2025. Predicting future risk of developing cognitive impairment using ambulatory sleep EEG: integrating univariate analysis and multivariate information theory approach. J. Alzheimer's Disease, 13872877251319742.

Hernandez, H., Baez, S., Medel, V., Moguilner, S., Cuadros, J., Santamaria-Garcia, H., Tagliazucchi, E., Valdes-Sosa, P.A., Lopera, F., Ochoagómez, J.F., 2024. Brain health in diverse settings: how age, demographics and cognition shape brain function. Neuroimage 295, 120636.

Hernandez, H., Santamaria-Garcia, H., Moguilner, S., Farina, F.R., Legaz, A., Prado, P., Cuadros, J., Gonzalez, L., Gonzalez-Gomez, R., Migeot, J., 2025. The exposome of healthy and accelerated aging across 40 countries. Nat. Med. 1–12.

Herzog, R., Barbey, F.M., Islam, M.N., Rueda-Delgado, L., Nolan, H., Prado, P., Krylova, M., Izyurov, I., Javaheripour, N., Danyeli, L.V., 2024a. High-order brain interactions in ketamine during rest and task: a double-blinded cross-over design using portable EEG on male participants. Transl. Psychiatry 14, 310.

Herzog, R., Mediano, P.A., Rosas, F.E., Luppi, A.I., Sanz-Perl, Y., Tagliazucchi, E., Kringelbach, M.L., Cofré, R., Deco, G., 2024b. Neural mass modeling for the masses: democratizing access to whole-brain biophysical modeling with FastDMF. Network Neurosci. 8, 1590–1612.

Herzog, R., Rosas, F.E., Whelan, R., Fittipaldi, S., Santamaria-Garcia, H., Cruzat, J., Birba, A., Moguilner, S., Tagliazucchi, E., Prado, P., Ibanez, A., 2022. Genuine high-order interactions in brain networks and neurodegeneration. Neurobiol. Dis. 175, 105918.

Ibanez, A., Kringelbach, M.L., Deco, G., 2024a. A synergetic turn in cognitive neuroscience of brain diseases. Trends Cogn. Sci.

Ibanez, A., Maito, M., Botero-Rodriguez, F., Fittipaldi, S., Coronel, C., Migeot, J., Lacroix, A., Lawlor, B., Duran-Aniotz, C., Baez, S., 2024b. Healthy aging meta-analyses and scoping review of risk factors across Latin America reveal large heterogeneity and weak predictive models. Nat. Aging 4, 1153–1165.

Ibanez, A., Melloni, L., Świeboda, P., Hynes, W., Ikiz, B., Ayadi, R., Thioye, M., Walss-Bass, C., Güntekin, B., Mishra, J., 2024c. Neuroecological links of the exposome and one health. Neuron 112, 1905–1910.

Jansen, B.H., Rit, V.G., 1995. Electroencephalogram and visual evoked potential generation in a mathematical model of coupled cortical columns. Biol. Cybern. 73, 357–366.

Jia, X., Fan, J., Wu, X., Cao, X., Ma, L., Abdelrahman, Z., Zhao, F., Zhu, H., Bizzarri, D., Akker, E.B.V.D., 2024. A novel metabolomic aging clock predicting health outcomes and its genetic and modifiable factors. Adv. Sci. 11, 2406670.

Kowalczyk, N., Shi, F., Magnuski, M., Skorko, M., Dobrowolski, P., Kossowski, B., Marchewka, A., Bielecki, M., Kossut, M., Brzezicka, A., 2018. Real-time strategy video game experience and structural connectivity–a diffusion tensor imaging study. Hum. Brain Mapp. 39, 3742–3758.

Laubenbacher, R., Mehrad, B., Shmulevich, I., Trayanova, N., 2024. Digital twins in medicine. Nat. Comput. Sci. 4, 184–191.

Le, T.T., Kuplicki, R., Yeh, H.-W., Aupperle, R.L., Khalsa, S.S., Simmons, W.K., Paulus, M. P., 2018. Effect of ibuprofen on BrainAGE: a randomized, placebo-controlled, dose-response exploratory study. Biol. Psychiatry: Cognit. Neurosci. Neuroimaging 3, 836–843.

Leake, I., 2024. Brain functional networks and psychiatric disorders. Nat. Rev. Neurosci. 25, 450.

Lee, H., Chung, M. K., Kang, H., Kim, B.-N., Lee, D. S., 2011. Discriminative persistent homology of brain networks. In: 2011 IEEE International Symposium on Biomedical Imaging: From Nano to Macro. IEEE, pp. 841-844.

Legaz, A., Altschuler, F., Gonzalez-Gomez, R., Hernández, H., Baez, S., Migeot, J., Fittipaldi, S., Medel, V., Maito, M.A., Godoy, M.E., Moguilner, S., Cruzat, J., Coronel-Oliveros, C., Tagliazuchi, E., Santamaria Garcia, H., Farina, F.R., Reyes, P., Javandel, S., García, A.M., Deleglise, Á., Matallana, D.L., Avila-Funes, J.A., Slachevsky, A., Behrens, M.I., Custodio, N., Trujillo-Llano, C., Cardona, J.F., Barttfeld, P., Brusco, I.L., Bruno, M.A., Sosa Ortiz, A.L., Pina-Escudero, S.D., Takada, L.T., França Resende, E.D.P., Possin, K.L., Okada De Oliveira, M., Hu, K., Lopera, F., Lawlor, B., Valcour, V., Yokoyama, J.S., Miller, B., Ibañez, A., 2024. Structural inequality linked to brain volume and network dynamics in aging and dementia across the Americas. Nat. Aging.

Lewandowsky, S., Oberauer, K., 2020. Low replicability can support robust and efficient science. Nat. Commun. 11, 358.

Luppi, A.I., Mediano, P.A.M., Rosas, F.E., Allanson, J., Pickard, J.D., Williams, G.B., Craig, M.M., Finoia, P., Peattie, A.R.D., Coppola, P., Owen, A.M., Naci, L., Menon, D. K., Bor, D., Stamatakis, E.A., 2022a. Whole-brain modelling identifies distinct but convergent paths to unconsciousness in anaesthesia and disorders of consciousness. Commun. Biol. 5, 384.

Luppi, A.I., Mediano, P.A.M., Rosas, F.E., Holland, N., Fryer, T.D., O'Brien, J.T., Rowe, J. B., Menon, D.K., Bor, D., Stamatakis, E.A., 2022b. A synergistic core for human brain evolution and cognition. Nat. Neurosci. 25, 771–782.

Luppi, A.I., Rosas, F.E., Mediano, P.A., Menon, D.K., Stamatakis, E.A., 2024. Information decomposition and the informational architecture of the brain. Trends Cogn. Sci. 28, 352–368.

Lynn, C.W., Bassett, D.S., 2019. The physics of brain network structure, function and control. Nat. Rev. Phys. 1, 318–332.
Marek, S., Laumann, T.O., 2024. Replicability and generalizability in population psychiatric neuroimaging. Neuropsychopharmacology 50, 52–57.
Marek, S., Tervo-Clemmens, B., Calabro, F.J., Montez, D.F., Kay, B.P., Hatoum, A.S., Donohue, M.R., Foran, W., Miller, R.L., Hendrickson, T.J., Malone, S.M., Kandala, S., Feczko, E., Miranda-Dominguez, O., Graham, A.M., Earl, E.A., Perrone, A.J., Cordova, M., Doyle, O., Moore, L.A., Conan, G.M., Uriarte, J., Snider, K., Lynch, B.J., Wilgenbusch, J.C., Pengo, T., Tam, A., Chen, J., Newbold, D.J., Zheng, A., Seider, N. A., Van, A.N., Metoki, A., Chauvin, R.J., Laumann, T.O., Greene, D.J., Petersen, S.E., Garavan, H., Thompson, W.K., Nichols, T.E., Yeo, B.T.T., Barch, D.M., Luna, B., Fair, D.A., Dosenbach, N.U.F., 2022. Reproducible brain-wide association studies require thousands of individuals. Nature 603, 654–660.
Matziorinis, A.M., Gaser, C., Koelsch, S., 2023. Is musical engagement enough to keep the brain young? Brain Struct. Funct. 228, 577–588.
McGlinchey, E., Duran-Aniotz, C., Akinyemi, R., Arshad, F., Zimmer, E.R., Cho, H., Adewale, B.A., Ibanez, A., 2024. Biomarkers of neurodegeneration across the Global South. Lancet Healthy Longev. 5.
Mindlin, I., Herzog, R., Belloli, L., Manasova, D., Monge-Asensio, M., Vohryzek, J., Escrichs, A., Alnagger, N., Núñez, P., Gosseries, O., 2024. Whole brain modelling for simulating pharmacological interventions on patients with disorders of consciousness. Commun. Biol. 7, 1176.
Moguilner, S., Baez, S., Hernandez, H., Migeot, J., Legaz, A., Gonzalez-Gomez, R., Farina, F.R., Prado, P., Cuadros, J., Tagliazucchi, E., Altschuler, F., Maito, M.A., Godoy, M.E., Cruzat, J., Valdes-Sosa, P.A., Lopera, F., Ochoa-Gómez, J.F., Hernandez, A.G., Bonilla-Santos, J., Gonzalez-Montealegre, R.A., Anghinah, R., D'almeida Manfrinati, L.E., Fittipaldi, S., Medel, V., Olivares, D., Yener, G.G., Escudero, J., Babiloni, C., Whelan, R., Güntekin, B., Yirikoğullari, H., Santamaria-Garcia, H., Lucas, A.F., Huepe, D., Di Caterina, G., Soto-Añari, M., Birba, A., Sainz-Ballesteros, A., Coronel-Oliveros, C., Yigezu, A., Herrera, E., Abasolo, D., Kilborn, K., Rubido, N., Clark, R.A., Herzog, R., Yerlikaya, D., Hu, K., Parra, M.A., Reyes, P., García, A.M., Matallana, D.L., Avila-Funes, J.A., Slachevsky, A., Behrens, M.I., Custodio, N., Cardona, J.F., Barttfeld, P., Brusco, I.L., Bruno, M.A., Sosa Ortiz, A.L., Pina-Escudero, S.D., Takada, L.T., Resende, E., Possin, K.L., De Oliveira, M.O., Lopez-Valdes, A., Lawlor, B., Robertson, I.H., Kosik, K.S., Duran-Aniotz, C., Valcour, V., Yokoyama, J.S., Miller, B.L., Ibanez, A., 2024a. Brain clocks capture diversity and disparities in aging and dementia across geographically diverse populations. Nat. Med.
Moguilner, S., Baez, S., Hernandez, H., Migeot, J., Legaz, A., Gonzalez-Gomez, R., Farina, F.R., Prado, P., Cuadros, J., Tagliazucchi, E., Altschuler, F., Maito, M.A., Godoy, M.E., Cruzat, J., Valdes-Sosa, P.A., Lopera, F., Ochoa-Gómez, J.F., Hernandez, A.G., Bonilla-Santos, J., Gonzalez-Montealegre, R.A., Anghinah, R., D'almeida Manfrinati, L.E., Fittipaldi, S., Medel, V., Olivares, D., Yener, G.G., Escudero, J., Babiloni, C., Whelan, R., Güntekin, B., Yirikoğullari, H., Santamaria-Garcia, H., Lucas, A.F., Huepe, D., Di Caterina, G., Soto-Añari, M., Birba, A., Sainz-Ballesteros, A., Coronel-Oliveros, C., Yigezu, A., Herrera, E., Abasolo, D., Kilborn, K., Rubido, N., Clark, R.A., Herzog, R., Yerlikaya, D., Hu, K., Parra, M.A., Reyes, P., García, A.M., Matallana, D.L., Avila-Funes, J.A., Slachevsky, A., Behrens, M.I., Custodio, N., Cardona, J.F., Barttfeld, P., Brusco, I.L., Bruno, M.A., Sosa Ortiz, A.L., Pina-Escudero, S.D., Takada, L.T., Resende, E., Possin, K.L., De Oliveira, M.O., Lopez-Valdes, A., Lawlor, B., Robertson, I.H., Kosik, K.S., Duran-Aniotz, C., Valcour, V., Yokoyama, J.S., Miller, B.L., Ibanez, A., 2024b. Brain clocks capture diversity and disparity in aging and dementia. Res Sq.
Moguilner, S., García, A.M., Perl, Y.S., Tagliazucchi, E., Piguet, O., Kumfor, F., Reyes, P., Matallana, D., Sedeño, L., Ibáñez, A., 2021. Dynamic brain fluctuations outperform connectivity measures and mirror pathophysiological profiles across dementia subtypes: a multicenter study. Neuroimage 225, 117522.
Moguilner, S., Herzog, R., Perl, Y.S., Medel, V., Cruzat, J., Coronel, C., Kringelbach, M., Deco, G., Ibanez, A., Tagliazucchi, E., 2024c. Biophysical models applied to dementia patients reveal links between geographical origin, gender, disease duration, and loss of neural inhibition. Alzheimers Res. Ther. 16, 79.
Neri, M., Brovelli, A., Castro, S., Fraisopi, F., Gatica, M., Herzog, R., Mediano, P.A., Mindlin, I., Petri, G., Bor, D., 2025. A taxonomy of neuroscientific strategies based on interaction orders. Eur. J. Neurosci. 61.
Neri, M., Vinchhi, D., Ferreyra, C., Robiglio, T., Ates, O., Ontivero-Ortega, M., Brovelli, A., Marinazzo, D., Combrisson, E., 2024. HOI: a Python toolbox for high-performance estimation of Higher-Order Interactions from multivariate data. J. Open Sour. Software 9, 7360.
Pardoe, H.R., Cole, J.H., Blackmon, K., Thesen, T., Kuzniecky, R., Investigators, H.E.P., 2017. Structural brain changes in medically refractory focal epilepsy resemble premature brain aging. Epilepsy Res. 133, 28–32.
Parra-Rodriguez, M.A., Prado, P., Moguilner, S., Herzog, R.A., Birba, A., Santamaría-García, H.A., Tagliazucchi, E., Reyes, P.A., Cruzat, J.A., García, A.M., Whelan, R., Lopera, F., Ochoa, J.F., Anghinah, R., Ibáñez, A., 2022. The EuroLaD-EEG consortium: towards a global EEG platform for dementia, for seeking to reduce the regional impact of dementia. Alzheimers Dement. 18.
Parra, M.A., Baez, S., Allegri, R., Nitrini, R., Lopera, F., Slachevsky, A., Custodio, N., Lira, D., Piguet, O., Kumfor, F., Huepe, D., Cogram, P., Bak, T., Manes, F., Ibanez, A., 2018. Dementia in Latin America. Neurology 90, 222–231.
Patania, A., Vaccarino, F., Petri, G., 2017. Topological analysis of data. EPJ Data Sci. 6, 1–6.
Patow, G., Martin, I., Sanz perl, y., kringelbach, m. l. & deco, g., 2024. Whole-brain modelling: an essential tool for understanding brain dynamics. Nat. Rev. Methods Primers 4, 53.
Petri, G., Expert, P., Turkheimer, F., Carhart-Harris, R., Nutt, D., Hellyer, P.J., Vaccarino, F., 2014. Homological scaffolds of brain functional networks. J. R. Soc. Interface 11, 20140873.
Ponce-Alvarez, A., Deco, G., 2024. The Hopf whole-brain model and its linear approximation. Sci. Rep. 14, 2615.
Pope, M., Varley, T.F., Puxeddu, M.G., Faskowitz, J., Sporns, O., 2025. Time-varying synergy/redundancy dominance in the human cerebral cortex. J. Phys.: Compl. 6, 015015.
Prado, P., Birba, A., Cruzat, J., Santamaría-García, H., Parra, M., Moguilner, S., Tagliazucchi, E., Ibáñez, A., 2022. Dementia ConnEEGtome: towards multicentric harmonization of EEG connectivity in neurodegeneration. Int. J. Psychophysiol. 172, 24–38.
Prado, P., Medel, V., Gonzalez-Gomez, R., Sainz-Ballesteros, A., Vidal, V., Santamaría-García, H., Moguilner, S., Mejia, J., Slachevsky, A., Behrens, M.I., Aguillon, D., Lopera, F., Parra, M.A., Matallana, D., Maito, M.A., Garcia, A.M., Custodio, N., Funes, A.Á., Piña-Escudero, S., Birba, A., Fittipaldi, S., Legaz, A., Ibañez, A., 2023a. The BrainLat project, a multimodal neuroimaging dataset of neurodegeneration from underrepresented backgrounds. Sci. Data 10, 889.
Prado, P., Mejía, J.A., Sainz-Ballesteros, A., Birba, A., Moguilner, S., Herzog, R., Otero, M., Cuadros, J., Z-Rivera, L., O'byrne, D. F., Parra, M. and Ibáñez, A., 2023b. Harmonized multi-metric and multi-centric assessment of EEG source space connectivity for dementia characterization. Diagnosis, Assessment & Disease Monitoring, Alzheimer's & Dementia, p. 15.
Ranasinghe, K.G., Verma, P., Cai, C., Xie, X., Kudo, K., Gao, X., Lerner, H., Mizuiri, D., Strom, A., Iaccarino, L., la Joie, R., Miller, B.L., Gorno-Tempini, M.L., Rankin, K.P., Jagust, W.J., Vossel, K., Rabinovici, G.D., Raj, A., Nagarajan, S.S., 2022. Altered excitatory and inhibitory neuronal subpopulation parameters are distinctly associated with tau and amyloid in alzheimer's disease. eLife 11.
Richard, G., Kolskår, K., Ulrichsen, K.M., Kaufmann, T., Alnæs, D., Sanders, A.-M., Dørum, E.S., Sánchez, J.M., Petersen, A., Ihle-Hansen, H., 2020. Brain age prediction in stroke patients: Highly reliable but limited sensitivity to cognitive performance and response to cognitive training. NeuroImage: Clin. 25, 102159.
Robiglio, T., Neri, M., Coppes, D., Agostinelli, C., Battiston, F., Lucas, M., Petri, G., 2025. Synergistic signatures of group mechanisms in higher-order systems. Phys. Rev. Lett. 134, 137401.
Rogenmoser, L., Kernbach, J., Schlaug, G., Gaser, C., 2018. Keeping brains young with making music. Brain Struct. Funct. 223, 297–305.
Rosas, F.E., Mediano, P.A., Gastpar, M., Jensen, H.J., 2019. Quantifying high-order interdependencies via multivariate extensions of the mutual information. Phys. Rev. E 100, 032305.
Rosas, F.E., Mediano, P.A., Luppi, A.I., Varley, T.F., Lizier, J.T., Stramaglia, S., Jensen, H. J., Marinazzo, D., 2022. Disentangling high-order mechanisms and high-order behaviours in complex systems. Nat. Phys. 18, 476–477.
Sampaio-Baptista, C., Johansen-Berg, H., 2017. White Matter Plasticity in the Adult Brain. Neuron 96, 1239–1251.
Sampaio Filho, C.I., De Arcangelis, L., Herrmann, H.J., Plenz, D., Kells, P., Ribeiro, T.L., Andrade, J.R.J.S., 2024. Ising-like model replicating time-averaged spiking behaviour of in vitro neuronal networks. Sci. Rep. 14, 7002.
Santamaria-Garcia, H., Sainz-Ballesteros, A., Hernandez, H., Moguilner, S., Maito, M., Ochoa-Rosales, C., Corley, M., Valcour, V., Miranda, J.J., Lawlor, B., Ibanez, A., 2023. Factors associated with healthy aging in Latin American populations. Nat. Med. 29, 2248–2258.
Santoro, A., Battiston, F., Lucas, M., Petri, G., Amico, E., 2024. Higher-order connectomics of human brain function reveals local topological signatures of task decoding, individual identification, and behavior. Nat. Commun. 15, 10244.
Santoro, A., Battiston, F., Petri, G., Amico, E., 2023. Higher-order organization of multivariate time series. Nat. Phys. 19, 221–229.
Sanz Perl, Y., Fittipaldi, S., Gonzalez Campo, C., Moguilner, S., Cruzat, J., Fraile-Vazquez, M.E., Herzog, R., Kringelbach, M.L., Deco, G., Prado, P., Ibanez, A., Tagliazucchi, E., 2023. Model-based whole-brain perturbational landscape of neurodegenerative diseases. eLife 12.
Shen, E.H., Overly, C.C., Jones, A.R., 2012. The Allen Human Brain Atlas: comprehensive gene expression mapping of the human brain. Trends Neurosci. 35, 711–714.
Sizemore, A.E., Giusti, C., Kahn, A., Vettel, J.M., Betzel, R.F., Bassett, D.S., 2018. Cliques and cavities in the human connectome. J. Comput. Neurosci. 44, 115–145.
Smith, S.M., Vidaurre, D., Alfaro-Almagro, F., Nichols, T.E., Miller, K.L., 2019. Estimation of brain age delta from brain imaging. Neuroimage 200, 528–539.
Stefanovski, L., Triebkorn, P., Spiegler, A., Diaz-Cortes, M.-A., Solodkin, A., Jirsa, V., McIntosh, A.R., Ritter, P., 2019. Linking molecular pathways and large-scale computational modeling to assess candidate disease mechanisms and pharmacodynamics in Alzheimer's disease. Front. Comput. Neurosci. 13.
Stolz, B.J., Emerson, T., Nahkuri, S., Porter, M.A., Harrington, H.A., 2021. Topological data analysis of task-based fMRI data from experiments on schizophrenia. J. Phys.: Compl. 2, 035006.
Tian, Y.E., Cropley, V., Maier, A.B., Lautenschlager, N.T., Breakspear, M., Zalesky, A., 2023. Heterogeneous aging across multiple organ systems and prediction of chronic disease and mortality. Nat. Med. 29, 1221–1231.
Timme, N., Alford, W., Flecker, B., Beggs, J. M., 2011. Multivariate information measures: an experimentalist's perspective. *arXiv preprint arXiv:1111.6857*.
Treder, M.S., Shock, J.P., Stein, D.J., du Plessis, S., Seedat, S., Tsvetanov, K.A., 2021. Correlation constraints for regression models: Controlling bias in brain age prediction. Front. Psych. 12, 615754.
van den Heuvel, M.P., Sporns, O., 2019. A cross-disorder connectome landscape of brain dysconnectivity. Nat. Rev. Neurosci. 20, 435–446.

Varley, T.F., Sporns, O., Stevenson, N.J., Yrjölä, P., Welch, M.G., Myers, M.M., Vanhatalo, S., Tokariev, A., 2025. Emergence of a synergistic scaffold in the brains of human infants. Commun. Biol. 8, 1–13.
Verdi, S., Marquand, A.F., Schott, J.M., Cole, J.H., 2021. Beyond the average patient: how neuroimaging models can address heterogeneity in dementia. Brain 144, 2946–2953.
Wang, H.E., Triebkorn, P., Breyton, M., Dollomaja, B., Lemarechal, J.-D., Petkoski, S., Sorrentino, P., Depannemaecker, D., Hashemi, M., Jirsa, V.K., 2024. Virtual brain twins: from basic neuroscience to clinical use. Natl. Sci. Rev. 11.
Wang, Z., Liu, F., Shi, S., Xia, S., Peng, F., Wang, L., Ai, S., Xu, Z., 2023. Automatic epileptic seizure detection based on persistent homology. Front. Physiol. 14.
Wasserman, I., 2018. Topological data analysis. Annu. Rev. Stat. Appl. 5, 501–532.
Williams, P.L., Eer, R.D., 2010. Nonnegative decomposition of multivariate information. *arXiv preprint arXiv:1004.2515*.
Xia, M., Wang, J., He, Y., 2013. BrainNet viewer: a network visualization tool for human brain connectomics. PLoS One 8, e68910–e.
Yilmaz, D., Papiol, S., Keeser, D., Cole, J. H., Malchow, B., Schmitt, A., Falkai, P., Maurus, I., Roell, L. 2025. Brain age gap reduction following physical exercise mirrors negative symptom improvement in schizophrenia spectrum disorders. *medRxiv*, 2025.01. 08.24319554.
Yusuf, S., Baden, T., Prieto-Godino, L.L., 2014. Bridging the Gap: establishing the necessary infrastructure and knowledge for teaching and research in neuroscience in Africa. Metab. Brain Dis. 29, 217–220.
Zhang, J., Bauman, R., Shafiabadi, N., Gurski, N., Fernandez-Bacavaca, G., Sahoo, S.S., 2022. Characterizing brain network dynamics using persistent homology in patients with refractory epilepsy. AMIA Ann. Symp. Proc. 1244.
Zomorodian, A., Carlsson, G., 2004. Computing persistent homology. In: Proceedings of the Twentieth Annual Symposium on Computational Geometry, pp. 347–356.