



**Università
degli Studi
di Palermo**

AREA RICERCA E TRASFERIMENTO TECNOLOGICO
SETTORE DOTTORATI E CONTRATTI PER LA RICERCA
U. O. DOTTORATI DI RICERCA

Dottorato di Ricerca in Medicina Molecolare e Clinica

**Dipartimento di Promozione della Salute, Materno-Infantile, di Medicina Interna e
Specialistica di Eccellenza “G. D’Alessandro”**

Settore Scientifico Disciplinare (corrisponde a quello del Tutor) - ING-INF/05.

Multiscale Dynamics: from single neurons to large-scale networks.

Modeling and applications with a focus on Alzheimer’s Disease

**IL DOTTORE
Camille Mazzara**

**IL COORDINATORE
Antonino Tuttolomondo**

**IL TUTOR
Albert Comelli**

**CO TUTOR
Pierpaolo Sorrentino**

CICLO XXXVII

ANNO CONSEGUIMENTO TITOLO 2026.



List of publications and conference participation

Publications published in the framework of this thesis:

1. Mazzara, C., Gambino, G., Duma, G. M., Neri, M., Giglia, G., Piccoli, T., Guajana, F., Comelli, A., Tuttolomondo, A., Migliore, M., & Sorrentino, P. (n.d.). Brain fluidity as a function marker of tau-related neurodegeneration in Alzheimer's disease [Preprint]. medRxiv. <https://doi.org/10.1101/2025.07.04.25330744>
2. Mazzara, C., Ziaemehr, A., Lopez Troisi, E., Cipriano, L., Angiolelli, M., Sparaco, M., Quarantelli, M., Granata, C., Sorrentino, G., & H. M. (2025). Mapping brain lesions to conduction delays: The next step for personalized brain models in multiple sclerosis. *Human Brain Mapping*, 46(7), e70219. <https://doi.org/10.1002/hbm.70219>
3. Mazzara, C., & Migliore, M. (2023). A realistic computational model for the formation of a Place Cell. *Scientific Reports*, 13(1), 21763. <https://doi.org/10.1038/s41598-023-48183-5>

Participation to conferences and summer schools during the period of the thesis:

4. 34th Annual Computational Neuroscience Meeting, Florence, Italy, July 5–9, 2025. Poster presentation: Brain fluidity as a function marker of tau-related neurodegeneration in Alzheimer's disease.
5. 33rd Annual Meeting of the Organization of Computational Neurosciences, Natal, Brazil, July 20–24, 2024. Poster presentation: Mapping brain lesions to conduction delays: The next step for personalized brain models in Multiple Sclerosis.
6. FENS Forum 2024, Vienna, Austria, June 25–29, 2024. Poster presentation: Cellular model of a place cell formation.
7. Society for Neuroscience (SfN) Neuroscience 2022, San Diego, California, USA, November 11–17, 2022. Poster presentation: Place Cell's Model.
8. OHBM 2025 Annual Meeting, Brisbane, Australia, June 23–28, 2025. Exhibitor for EBRAINS Italy.
9. EBRAINS Brain Simulation Workshop, Bilbao, Spain, June 3–7, 2024. Workshop on Computational Neuroscience and the EBRAINS Cellular Level Model Platform (ECEMP).
10. EBRAINS Brain Simulation School 2023, Genova, Italy, May 19–24, 2023. Training on modelling neurons, circuits, and cognitive functions.
11. Human Brain Project Summit 2023, Marseille, France, March 28–31, 2023. Conference participation: Achievements and future of digital brain research.

Abstract and keywords

Understanding the brain's function and pathology necessitates a multiscale approach, as neurological disorders stem from disruptions at the cellular level that cascade to alter large-scale network dynamics. This thesis integrates computational modeling across micro- and macroscales to investigate neural dynamics in both health and disease, with a core focus on Alzheimer's disease (AD). The work is organized into three complementary studies.

First, we investigated the cellular mechanisms underlying the formation of hippocampal Place Cells (PCs). We developed a morphologically and biophysically realistic computational model of a CA1 pyramidal neuron to examine how it acquires spatially selective firing. The model demonstrates that place-field emergence results from the coordinated activation of two different inputs: a distal input from the entorhinal cortex (EC) and a proximal input from the CA3. This co-activation selectively potentiates specific synapses, leading the neuron to code for a cue location. The model reproduces key experimental observations, including place-field stability across trajectories, stability after environment rotation, and place-field remapping. To date, it represents the only cellular model that mechanistically explains PC formation with biophysical and morphological accuracy, suggesting a potential mechanism through which early hippocampal impairment in AD could disrupt spatial navigation.

Next, we studied Alzheimer's disease (AD) at the macroscale using source-reconstructed EEG from 28 patients and 29 healthy controls. We quantified *brain fluidity*, a measure of the brain's ability to flexibly reconfigure functional connectivity over time. AD patients showed frequency-specific disruptions: fluidity increased in the theta band but decreased in the beta band. Reduced beta-fluidity significantly correlated with higher cerebrospinal tau levels and predicted cognitive performance better than standard biochemical markers, indicating that loss of temporal flexibility is a signature of AD-related network disconnection.

Finally, we examined multiple sclerosis (MS). In 38 participants (18 MS and 20 controls), we combined MEG resting-state activity with MRI tractography and used large-scale brain models to estimate how tract lesions translate into conduction delays. Each brain region was modeled as a Stuart–Landau oscillator coupled by subject-specific connectomes. Through Bayesian model inversion, we showed that the inferred lesion–delay parameter strongly correlates with individual alpha-peak slowing in MEG and predicts clinical disability,

whereas total lesion volume alone does not. This provides the first tract-specific quantitative mapping between myelin damage and functional slowing.

Across these three studies, the thesis demonstrates how cellular alterations, loss of functional flexibility, and structural disconnection impair the timing and integration of neural information. The results provide a framework for the development of mechanistic biomarkers and suggest that multiscale models could contribute to individualized predictions of disease progression and therapeutic responses.

Keywords: Alzheimer's Disease, Spatial Navigation, Multiple Sclerosis, Functional Connectivity, Fluidity, Multiscale Modeling, Probabilistic Inference.

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Background

The adult human brain weighs 1400 grams on average. Within this wrinkled, jelly-like neural material, our memories, our experiences, and even our dreams emerge. It is through the electrochemical impulses of its intricate neural circuits that our identity takes shape. The brain contains tens of billions of neurons and around 100 trillion connections between them. Somehow, this vast biological network is what we are. The reason we know this is true is because damages to our brain can change us entirely. We can change our decision-making, lose our ability to talk, understand simple concepts, and so on. For example, let's take the story of Phineas Gage, who was a young railroad worker in the 1880s. An explosion blew an iron rod through his head, and the rod clattered to the ground 50 yards away. He did not die, he did not even lose consciousness, but his personality changed entirely. Instantly, as soon as this part of this prefrontal lobe was stripped away, he became a different person. The sweet young man that everyone liked didn't exist anymore, he started to cuss, he became more aggressive, violent, a pathological gambler, a completely different person. When our biology changes, we change. We are tied to our biology and there is no way we can escape that. We have learned these lessons over hundreds of years of strokes, tumors, traumatic injuries. This is how we know that the brain is the densest and truest representation of ourselves. How the interplay of billions of neurons and glial cells define our identity? Understanding how the brain works is not only fascinating from a scientific perspective but also crucial from a clinical point of view. When these delicate neural systems are disrupted by disease, trauma, or degeneration, the very essence of a person can change. Studying these mechanisms allows us to better understand the biological basis of neurological and psychiatric disorders, to develop more effective treatments, and to improve patients' quality of life. Nevertheless, understanding a brain disease by looking at just one scale is limiting. The brain is an extremely complex system, and what we observe at the macroscopic level, as a behavior, is always the result of deeper, nested mechanisms acting at the macro-, meso- and micro-scales. Focusing on only one level is oversimplified and limiting. To truly understand a pathology, we need to dig deeper, explore what happens across different scales, and try to connect them. This is why, while this thesis primarily focuses on investigating the static and dynamic properties of brain activity in Alzheimer's patients compared to healthy controls, it also looks beyond large-scale dynamics. The functional alterations observed in Alzheimer's disease are only the "tip of the iceberg". Since spatial navigation is affected by Alzheimer's disease, this

work is complemented by a biophysical model of place cells to explore the processes at the cellular level. Throughout this work, a multiscale perspective has been adopted to investigate neural dynamics at different levels of organization. This approach aims to bridge the gap between cellular mechanisms, large-scale network activity, and behavior. By integrating these different scales, the thesis seeks to provide a more comprehensive understanding of the processes underlying neurodegeneration, moving beyond the limitations of a single-scale analysis.

1. Introduction

The human brain is widely regarded as one of the most fascinating and complex dynamical systems in nature (1–4). Its activity cannot be fully understood by analyzing components in isolation, because its functioning emerges from continuous and nonlinear interactions unfolding across multiple levels, from molecular mechanisms and single neurons to the coordinated dynamics of large-scale brain networks (5–7). This complexity arises from many sources: the diversity of neuronal types with distinct properties, the heterogeneity of synaptic mechanisms, the plasticity that ensures continuous adaptation, and the hierarchical organization of circuits embedded within broader networks. We identify at least 8 distinct anatomo-functional levels: bio-molecules, simple subcellular structures (membranes, calcium stores, etc.), complex subcellular structures (synapses, dendritic spines, etc.), aggregates of subcellular structures, cells, local multicellular aggregates (local neuronal microcircuits), interconnected microcircuits, and large-scale networks (8) (Fig.1). These levels can be referred to as microscale, mesoscale, and macroscale. At the microscopic scale, single neurons generate electrical spikes and local synaptic currents that represent the most elementary units of communication in the nervous system (9). At the mesoscopic level, populations of neurons interact to produce local field potentials and oscillations that reflect their cooperative behavior (10). And finally, at the macroscopic level, brain regions coordinate their activity, expressed in Electroencephalography (EEG) and magnetoencephalography (MEG) rhythms, and Functional Magnetic Resonance Imaging (fMRI) co-activations, to support cognition, perception, and behavior (11).

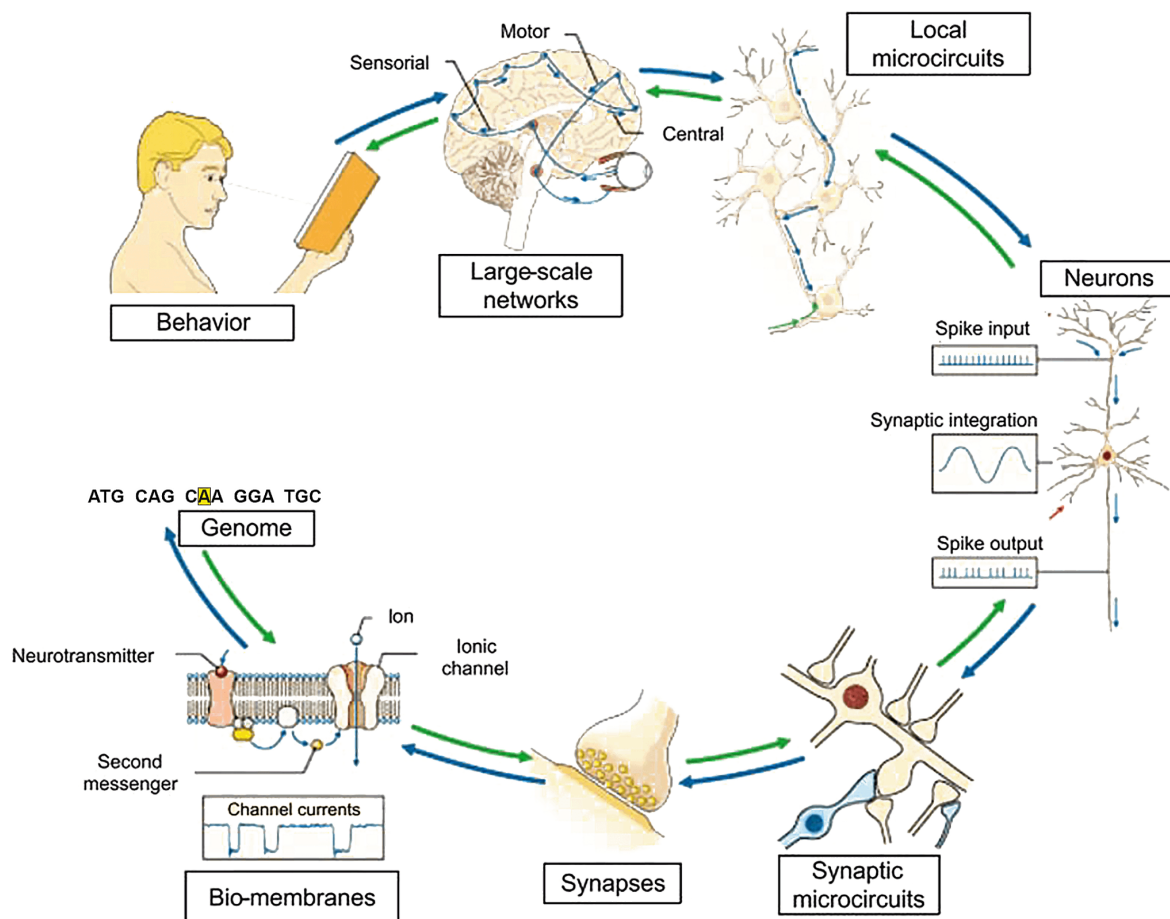


Figure 1. The multiscale organization of the brain. Multiple levels of brain organization, from molecules to cells, circuits and behaviour. Taken from D'Angelo et al., 2017 (8).

Despite decades of research, how the brain generates thoughts, stores memories, creates opinions, perceives sensations and makes all of this conscious, remains unclear. For example, it's not yet fully understood how the brain responds to stimuli whose duration spans several orders of magnitude, from milliseconds in sensory processing to hours, days, or even years in learning and memory. The same system that enables a rapid reflex also supports the lifelong storage of experiences. Similarly, our knowledge of how the brain computes information across spatial scales, from the activity of individual synapses to the coordination of distant cortical regions, and integrates these levels to produce coherent behavior remains limited (12). These capacities are not merely of theoretical interest, they are also highly relevant from a translational perspective since neurological and psychiatric disorders often impair the brain's ability to process information across time and space, leading to deficits and abnormalities in perception and cognitive functions as attention, language, working memory, motor control and so on (13).

Explaining how cellular-level processes give rise to cognitive functions and how large-scale network dynamics feed back to influence individual neurons is therefore particularly relevant in the study of neurodegenerative disorders, where disruptions at one level, such as molecular alterations, synaptic dysfunction, or circuit disorganization, can cascade across scales and manifest as abnormal network oscillations, impaired connectivity, and ultimately cognitive or behavioral deficits. For example, pathological changes at the molecular or cellular level, such as demyelination or neuronal loss, can lead to altered network oscillations and cognitive dysfunction (14). Conversely, abnormal large-scale rhythmic activity, such as hypersynchronous oscillations in epilepsy or slowed brain waves in dementia, often reflects underlying circuit or cellular anomalies (15–17). Healthy brain function relies on precise temporal coordination of neural activity, when these coordinating rhythms are compromised, function breaks down.

Each one of these levels has its own complexity and can be explored through specific techniques. The properties observed at one level can be used to predict those of the higher hierarchical level or can be demonstrated by mechanisms at the lower level, but longer jumps across scales (e.g. from molecules to brain) are arduous (8). From a physical perspective, it is rare for a single system to integrate such a wide range of functions across scales within a unified framework. This implies that no single theoretical or computational model can capture brain dynamics in their entirety. Instead, different modeling approaches are required at different levels of organization (8,18). Detailed biophysical models are needed to explain how ionic currents and synaptic integration give rise to neuronal firing; intermediate-scale models describe how local circuits generate oscillations and coordinate activity; and large-scale network models capture how distributed brain regions interact to support cognition and behavior. Bridging these complementary approaches is crucial not only for understanding how neural assemblies coordinate their activity across spatial and temporal scales, but also for uncovering how disruptions at one level, from ion channel dysfunction to altered network connectivity, can cascade across levels and manifest as disease (19,20). For this reason, studying brain dynamics across multiple scales is not only an academic pursuit but also a powerful way to understand disease mechanisms and develop biomarkers or therapeutic strategies. Depending on the specific question, the relevant scale of analysis may change. From a technical perspective, this requires choosing the most appropriate experimental techniques and computational models to uncover the generative mechanisms underlying the process of interest.

This thesis adopts a multiscale approach to investigate brain dynamics in both health and disease, with a primary focus on Alzheimer's disease (AD). AD is a progressive neurodegenerative disorder that profoundly alters brain structure and function, disrupting memory, spatial navigation, and other cognitive domains (21–25). A central part of this work is dedicated to analyzing large-scale EEG activity to identify dynamic network biomarkers of neurodegeneration. Specifically, the concept of brain fluidity is introduced to quantify the brain's capacity for flexible reconfiguration of functional connectivity over time. In AD patients, this balance of network fluidity is disrupted in a frequency-specific manner: there is an excess of low-frequency (theta-band) fluidity alongside a marked reduction in higher-frequency (beta-band) fluidity. Crucially, this loss of beta-band adaptability correlates with elevated tau pathology and predicts cognitive decline, linking microscopic molecular pathology to macroscopic network dysfunction. By capturing the temporal variability of inter-regional interactions, this EEG-based marker offers a novel perspective on AD as a network disconnection syndrome and illustrates how neurodegenerative processes compromise the brain's dynamic flexibility.

A comprehensive understanding of the large-scale neural dynamics implicated in AD inherently necessitates an equally thorough examination of the underlying mechanisms at lower spatiotemporal brain scales. A prime example is spatial navigation, which is among the earliest and most severely affected cognitive domains in AD, tightly coupled to dysfunction of the hippocampus and related structures. To interrogate this cognitive domain, the endeavor outlined here includes the development of a detailed biophysical model of a hippocampal CA1 pyramidal neuron that self-organizes its synaptic inputs to become a place cell, reproducing the stable, location-specific firing observed in empirical investigations. Said model provides a mechanistic account of how dendritic integration and synaptic plasticity afford such neurons to encode spatial cues, and offers invaluable insights into the cellular-level processes that may be compromised early in AD.

The combined insights derived from the above mentioned micro and macroscale inquiries into the perturbations potentially implicated in AD - namely large-scale network analyses in AD and single-neuron modeling of place cells - coalesce to form a unified and invaluable multiscale perspective of AD. The former captures how neurodegeneration affects brain-wide dynamics, and the latter delineates neurobiological mechanisms which underlie the cells potentially involved in said disruptions. By integrating the findings attained through the abovementioned micro and macroscale AD investigations, with the supplementary inquiries

into the hierarchical organization of the nervous system we can attempt to establish a granular understanding of AD across brain scales.

To complement our comprehension about large-scale networks organization we employ a whole-brain modeling strategy. This approach allows for the integration of personalized anatomical and physiological information into a mechanistic model that effectively simulates realistic brain activity (virtual brain), subject to its network dynamics. Disruption of such dynamics can lead to pathological brain rhythms which are reflected as features of the canonical frequency bands. Since the fluidity-related feature was not yet found in AD, our virtual brain use case had to be based on another neuropathology with established network synchrony disruption. Multiple sclerosis (MS) is known to cause decreases in the alpha band frequency peak. Based on this setup, we investigated how demyelinating lesions in MS influence conduction delays and large-scale oscillatory dynamics. This additional study substantiates the central idea of this endeavor: Top-down -slow- oscillations generated by large neuronal populations can influence and organize faster, more localized neural events, while bottom-up (i.e. microscale or cellular) processes shape and modulate macroscopic network activity. Such a hierarchical lens can thus lend itself to deepening our understanding of how complex brain activity is coordinated and how its disruption leads to disease.

1.1 Neural Signals at Different Scales

Neural activity can be measured at multiple spatial and temporal scales, with each offering a singular window into brain function. A rigorous interpretation of brain dynamics thus necessitates a clear understanding of the biological underpinnings of said scale-bound oscillations and the constraints inherent to their measurement.

Microscale: Neuronal Spikes, Synaptic Potentials, and Intracellular Recordings

At the microscopic scale reside the brain's fundamental computational and communicatory units: individual neurons and their synaptic connections. Attaining a rigorous understanding of dynamics present at this level is paramount, as it forms the biological substrate upon which all higher-order cognitive functions are ultimately constructed. In brief, microscale activity encompasses the generation and propagation of action potentials (spikes), the integration of

synaptic potentials, and the intrinsic electrical properties of neuronal membranes. These phenomena are assessed using high-resolution electrophysiological and optical techniques.

Neuronal spikes, or action potentials, are rapid, all-or-none electrical signals that constitute the primary instrument of long-range communication in the nervous system. It occurs when the membrane depolarization reaches a critical threshold, triggering a precise sequence of opening and closing of voltage-gated ion channels. This process generates an electrical signal capable of transmitting information efficiently over long distances within the nervous system. These stereotyped signals transmit information rapidly along the axons and represent the basic building blocks of neuronal communication. Their informational value often depends less on how many spikes occur than on when they occur relative to ongoing network rhythms. Recordings obtained with intracellular or fine microelectrodes allow the detection of spikes from single neurons, providing highly precise temporal information about their activity.

Spiking activity paints a thin veneer with regards to the overall picture of neural function. Intriguingly, the brain's vast energetic expenditure is devoted not primarily to action potential generation but to the production of synaptic potentials: graded changes in membrane voltage resulting from neurotransmitter release. Unlike the all-or-none action potential, these are graded, local, and often subthreshold. Excitatory postsynaptic potentials (EPSPs)—typically mediated by glutamate—depolarize the postsynaptic membrane, moving the neuron closer to its firing threshold. Conversely, Inhibitory postsynaptic potentials (IPSPs)—often mediated by GABAergic transmission—hyperpolarize the membrane, moving it further from the threshold. These potentials, which arise from the opening of ligand-gated ion channels, decay with distance but summate both spatially and temporally. This complex integration of synaptic potentials ultimately determines whether or not an action potential will be generated.

Intracellular recordings offer the most direct window into these fundamental processes. Techniques such as sharp microelectrode recordings and the patch-clamp method allow for the granular measurement of a neuron's membrane potential and ionic currents, often with millivolt and picoampere resolution. Patch-clamp has revolutionized cellular neurophysiology by enabling not only whole-cell recordings but also single-channel measurements, enabling researchers to directly observe the stochastic opening and closing of individual ion channels. Supplementary optical methods such as calcium imaging, extend these insights to larger neuronal populations, thereby synthesizing single-neuron activity and population (i.e. mesoscale) dynamics. Despite laying the foundation of subpopulation

dynamics, single-unit dynamics is -by itself- insufficient in a thorough portrayal of brain function, as said activity cannot be directly translated into the emergent coordination of activity which dominates whole-brain dynamics.

Mesoscale: Local Field Potentials, Multi-Unit and Single-Unit Activity

At the mesoscale level, neuronal activity is examined not in isolation but as the emergent property of coordinated interactions within local microcircuits. This scale represents a critical link between the cellular dynamics of single neurons and the large-scale activity patterns observed across distributed brain networks. Mesoscale signals reveal how neuronal populations integrate synaptic inputs, synchronize their activity, and generate collective rhythms.

One of the principal tools for studying this level of organization is the local field potential (LFP). LFPs reflect the extracellular signals generated by the combined synaptic activity of many neurons within a local circuit. Rather than isolating the output of single cells, they capture how populations of neurons integrate incoming inputs and coordinate their responses. LFPs are not just the average of multiple spikes, but instead represent the underlying input and processing activity of the network. Because they mirror collective synaptic processes, LFPs often show a stronger relationship to the BOLD signal in fMRI than to action potentials, highlighting their relevance for linking mesoscopic neural dynamics to macroscopic imaging signals. Recordings can be obtained using intracortical electrodes or electrocorticography (ECoG) grids placed on the cortical surface, revealing the pooled activity of local neuronal assemblies. The primary contributors to these signals are transmembrane synaptic currents, although other cellular sources can shape the measured field. LFPs provide a mesoscopic perspective on oscillations and circuit dynamics. However, their spatial resolution is inherently limited (typically spanning only a few hundred microns to a few millimeters) and their interpretation can be challenging, since LFPs reflect a mixture of different physiological sources, primarily synaptic currents but also contributions from action potentials near the electrode, intrinsic membrane currents, and even glial or volume-conducted signals, all of which together shape the extracellular field.

Complementary to LFPs are measures of *multi-unit activity (MUA)* and *single-unit activity (SUA)*, which capture neuronal spiking output with high temporal precision. MUA represents the aggregate spiking of a small population of neurons near the electrode, offering a direct

readout of local network output. SUA isolates the activity of individual neurons from extracellular recordings, allowing researchers to examine how single cells encode information within a broader circuit context. Together, these signals provide complementary insights: while LFPs reveal the integrative and oscillatory properties of local networks, MUA and SUA report on the discrete outputs that drive communication across circuits.

Mesoscale recordings are essential for understanding how micro-level events scale up to influence network dynamics. Furthermore, mesoscale activity forms the physiological substrate of macroscopic signals such as EEG and MEG, which emerge from the summation of many local field potentials across brain regions. As such, studying mesoscale signals is not only key to understanding fundamental brain function but also critical for identifying how these processes break down in neurological and psychiatric disorders, where alterations in local network dynamics often precede and contribute to large-scale dysfunction.

Macroscale: EEG, MEG, fMRI, PET

At the macroscopic level, brain activity is captured as the emergent result of large-scale interactions among distributed neuronal populations and networks. Unlike micro- and mesoscopic techniques, which provide detailed information about individual neurons or local circuits, macroscale methods such as electroencephalography (EEG), magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI), and positron emission tomography (PET) allow the non-invasive investigation of whole-brain dynamics in humans. These approaches reveal how spatially distant brain regions coordinate their activity to support cognition, behavior, and perception, and are indispensable for both basic neuroscience and clinical research.

EEG and *MEG* record large-scale brain signals by detecting, respectively, voltage fluctuations and magnetic fields at the scalp. These signals arise mainly from the synchronous activity of cortical pyramidal neurons, whose geometry allows their postsynaptic currents to sum when aligned. EEG and MEG thus provide a window onto the coordinated dynamics of vast neuronal populations rather than the activity of individual cells. Their main strength is their millisecond temporal resolution, though their spatial precision is more limited. EEG or MEG signals can be thought of as capturing the overall sound of an orchestra without identifying the individual instruments: it reveals global changes in brain state, such as the transitions between wakefulness, sleep stages, or seizure activity, but offers little detail about which

circuits or cell types are involved. Clinically, EEG has long been indispensable for diagnosing epilepsy, sleep disorders, and encephalopathies. MEG, which measures the magnetic fields generated by the same currents, is more sensitive to tangential sources. Both methods capture not neuronal spiking itself, but the temporal organization of inputs and network-level processing that underlies large-scale brain rhythms. Importantly, both EEG and MEG are noninvasive techniques, which makes them safe and repeatable tools for studying human brain activity over time, an essential feature for both clinical practice and research.

In contrast to EEG and MEG, which directly record electrical or magnetic signals, *fMRI* and *PET* measure neuronal activity indirectly. *fMRI* detects changes in blood oxygenation (the BOLD signal), while *PET* uses radiolabeled tracers to monitor glucose consumption. These measures reflect the energy demands of large groups of neurons. As a result, *fMRI* and *PET* provide excellent spatial coverage across the entire brain but have limited temporal resolution. They are indispensable tools for mapping large-scale networks and linking patterns of activation to behavior or pathology. A useful analogy is that *fMRI* resembles an infrared image of an orchestra: it reveals which sections are most active at a given moment but cannot capture the fine timing of the music. Thus, while *fMRI* and *PET* cannot track rapid neural dynamics, they are invaluable for identifying which brain regions are engaged during tasks and for studying large-scale functional connectivity. These methods have been central to uncovering the networks supporting functions such as language, memory, and emotion, and to characterizing disease-related alterations in conditions including Alzheimer's disease, Parkinson's disease, and various psychiatric disorders.

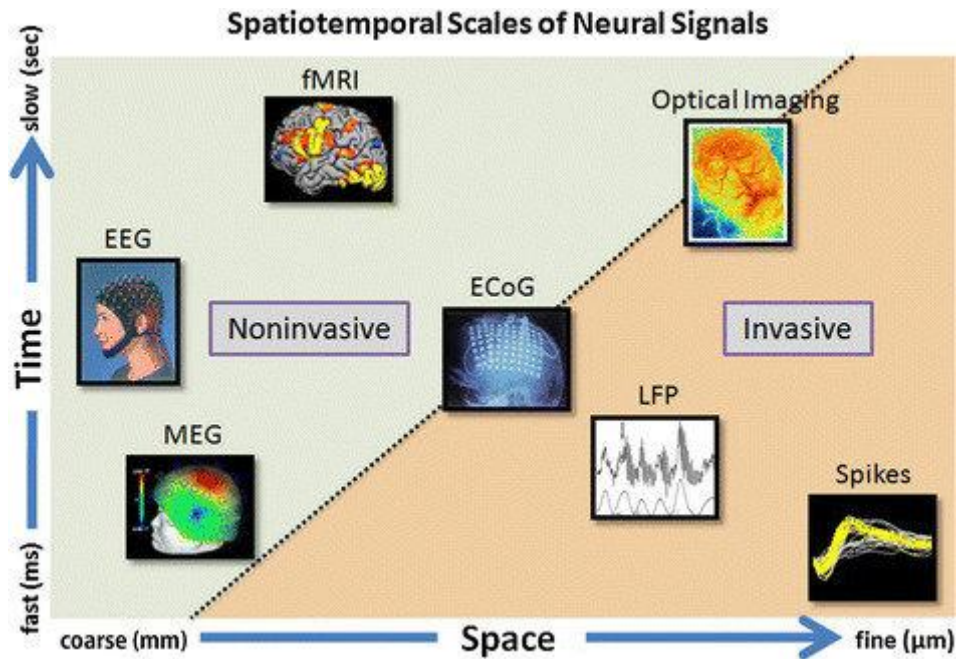


Figure 2. Neural Signals across different spatiotemporal scales. Taken from Kim et al. 2015 (26).

1.2 Computational models across different scales

We have seen how brain activity can be measured using different techniques, each providing insights into different aspects and facets of neural activity at various scales. Each type of measurement has its own strengths and limitations. What can be said with certainty is that none of them can provide broad-spectrum information about neural mechanisms, and even when combining signals recorded at different scales, understanding the complexity of how the brain works remains a challenging task. To understand the relationship between brain structure, function, and dynamics and to uncover the mechanisms underlying a specific behavior, such as identifying which circuits are activated and determining their role within a larger system, researchers have increasingly begun to use computational models.

The choice of computational model depends on the scientific question being asked: which process is being studied, which mechanism is to be understood, and at which scale? A model can be considered a good model for its predictive accuracy or for its ability to replicate biological phenomena accurately (27). Depending on the aim, the level of abstraction of the model can vary. Based on the specific research question and the level of detail required, we may choose to use more biophysical models or more phenomenological ones.

The first ones aim to reproduce physiological processes with high fidelity. Although these models offer a more detailed representation of neuronal function, they often involve greater complexity and higher computational costs. Phenomenological models, instead, capture emergent dynamics without explicitly replicating underlying mechanisms. These models provide a valuable alternative because they can represent key dynamics with relative simplicity, making them suitable for large-scale simulations and for exploring emergent properties of neural networks.

Despite this well-defined distinction, the reality is that we need to remember that even the most sophisticated biophysical models remain a simplification of reality: they capture the essential features of neuronal activity but cannot fully reproduce the complexity of biological neurons, which possess a multitude of ion channels, extremely complex arborization, and crucial interactions with glial cells.

To understand brain processing, it is necessary to uncover the multilevel organization of neural dynamics. This is possible by developing models that bridge microscopic neural processes with whole-brain activity. Because neural phenomena unfold across multiple spatial and temporal scales, from ion channel dynamics and synaptic transmission to network oscillations and large-scale brain activity, no single model can capture the full range of brain function.

Models at the Microscale

At the finest scale, computational models describe how single neurons work and the underlying biophysical and cellular mechanisms (for example how the membrane potential changes over time or how electrical signals propagate along dendrites and axons). As mentioned earlier, these models fall into two categories: biophysical and phenomenological, which differ in their level of biological detail and in their goals. Microscale *biophysical* models aim to reproduce the electrophysiology of neurons and synapses with maximal realism. Classic examples include the Hodgkin–Huxley model (28), morphologically detailed multi-compartment neuron models that incorporate the anatomical structure of the dendrites, soma, and axon (29–31), and Markov models of ion channel kinetics, which describe the stochastic opening and closing of individual channels (32)

Hodgkin–Huxley model represents one of the most important discoveries in computational neuroscience, formulated in 1952 based on voltage-clamp experiments on the squid giant axon. This model provides a quantitative description of the ionic mechanisms underlying the generation and propagation of the action potential. In this framework, the neuronal membrane is treated as an electrical circuit composed of a membrane capacitance and voltage-dependent conductances for sodium (Na^+) and potassium (K^+), together with a passive leakage conductance (primarily associated with chloride (Cl^-) ions). The temporal evolution of the membrane potential V_m is described by the fundamental membrane equation:

$$C_m \frac{dV_m}{dt} = - \left[g_{Na} m^3 h (V_m - E_{Na}) + g_K n^4 (V_m - E_K) + g_L (V_m - E_L) \right] + I_{ext}$$

Here, C_m is the membrane capacitance, g_{Na} , g_K , and g_L are the maximal conductances of sodium, potassium, and leak channels, respectively, and E_{Na} , E_K , and E_L are their reversal potentials. I_{ext} denotes externally applied current. The terms m , h , and n are gating variables that represent the probabilities that specific channel gates are in their open or closed states and evolve according to first-order kinetics:

$$\tau_m \frac{dm}{dt} = m_\infty(V) - m$$

$$\tau_h \frac{dh}{dt} = h(V) - h$$

$$\tau_n \frac{dn}{dt} = n_\infty(V) - n$$

where τ_i are the voltage-dependent time constants and $x_\infty(V)$ (with $x=m, h, n$) are the steady-state activation or inactivation functions derived from experimental fits. The sodium current is controlled by the gating variables m (activation) and h (inactivation), while n governs the activation of potassium channels. Together, these equations describe how changes in membrane voltage cause the sequential opening and closing of voltage-gated ion channels. A rapid increase in sodium conductance opens voltage-gated sodium channels, triggering an influx of sodium ions that generates the depolarizing phase of the action potential. This is followed by the delayed activation of potassium conductance, whose outward current drives repolarization and returns the membrane potential toward its resting level.

Building upon this foundational framework, *multicompartmental models* extend the Hodgkin–Huxley formalism to include the spatial complexity of real neurons. Instead of representing a neuron as a single isopotential unit, these models divide it into interconnected compartments representing distinct anatomical regions such as the soma, dendrites, and axon. Each compartment is described by the cable equation, which governs how voltage spreads along a passive dendritic tree:

$$\frac{\partial V(x,t)}{\partial t} = -\frac{1}{R_m C_m} V(x,t) + \frac{\lambda^2}{C_m} \frac{\partial^2 V(x,t)}{\partial x^2} + \frac{I_{ion}(x,t)}{C_m}$$

Here, R_m is the membrane resistance, C_m the capacitance, and λ the space constant describing how far voltage spreads passively. $I_{ion}(x,t)$ represents active ionic currents modeled by Hodgkin–Huxley-type dynamics. Thanks to this detailed spatial description, it becomes possible to simulate how synaptic inputs arriving on distal dendrites combine and influence the soma’s ability to generate action potentials. It also allows modeling the back-propagation of action potentials from the soma into the dendritic branches. Such models have revealed, for instance, how dendritic spikes, compartmentalized synaptic integration, and spatially distributed plasticity rules contribute to a neuron’s input–output transformation, phenomena that single-compartment models cannot capture. However, the detailed representation of thousands of ionic channels and multiple compartments is computationally demanding, often requiring high-performance computing resources even to simulate small networks. Despite these challenges, biorealistic models remain indispensable tools for linking molecular and cellular mechanisms to emergent neuronal dynamics. They allow researchers to explore how perturbations at the micro-level, such as changes in ion channel density, dendritic morphology, or synaptic kinetics, give rise to emergent properties of neural computation.

Phenomenological models at this scale, such as the leaky integrate-and-fire (LIF) model (33,34) or the Izhikevich neuron model (35), focus instead on capturing essential input–output behavior using reduced equations. The *LIF model* represents the neuron as a passive electrical circuit that integrates incoming inputs until a threshold is reached, at which point it triggers a spike. Extensions such as the quadratic integrate-and-fire and exponential integrate-and-fire models reproduce more realistic spike initiation dynamics while remaining simple. The *Izhikevich model* combines biological plausibility with computational efficiency and can reproduce a wide variety of neuronal firing patterns using only a few equations. These simplified models sacrifice mechanistic detail but capture essential aspects of neuronal

dynamics, making them particularly useful for linking single-neuron behavior to network-level computations. They forego detailed representations of ion channel kinetics but enable simulations of large neuronal networks while preserving core firing dynamics. Although they lack explanatory depth regarding the underlying mechanisms, their computational tractability makes them precious for studying emergent network behavior across many neurons.

From Single Neurons to Population Dynamics

As we move from single neurons to larger populations, the focus shifts toward understanding how local ensembles and entire brain regions coordinate their activity to generate coherent macroscopic dynamics. Modeling at these scales requires a conceptual and methodological transition: from detailed ionic and cellular descriptions to more abstract, population-based formulations that characterize the collective behavior of large neuronal ensembles. These mesoscale and macroscale models constitute the foundation for whole-brain simulations and for linking neural mechanisms to measurable signals such as EEG, MEG, and fMRI.

Despite advances in high-performance computing, simulating in a realistic manner neural circuits that include hundreds of millions of neurons, their synapses, and all their intricate details is still out of the question. Moreover, our understanding of the neurobiological mechanisms underlying the activity of specific neuronal circuits is limited, especially when it comes to humans. Therefore, it is reasonable to develop models that maintain a reasonable balance between biological and computational plausibility. In this context, *neural mass models (NMMs)* come into play. Instead of modeling individual neurons and their complex synaptic connections, NMMs capture the emergent properties of a neuronal population, allowing for simpler yet powerful simulations capable of describing large-scale dynamics at both regional and network levels (18,19,36).

They conceptualize cerebral regions as a ‘mass’ of neurons: instead of explicitly modeling each neuron, they capture the average behavior of neuronal populations through a small number of macroscopic variables, such as mean membrane potential and firing rate. A common example of this kind of simplification is the mean-field theory, in which the dynamics of a large collection of microscopic units are approximated by the dynamics of an “average” unit.

Neural mass models are not uniform in their level of biological detail. They differ from biophysically grounded formulations to highly phenomenological descriptions, forming a family of approaches that range from models derived from cellular and synaptic mechanisms to simplified formulations that capture only emergent population dynamics.

Between the biophysical neural mass models we can find the *Jansen–Rit model* (37,38), which describes a cortical column consisting of pyramidal cells and inhibitory interneurons with distinct time constants, using explicit synaptic response functions and a sigmoidal transfer function to map mean membrane potential to firing rate. It incorporates physiologically interpretable parameters, such as synaptic time constants and EPSP/IPSP amplitudes, providing an approximate representation of the mechanisms underlying cortical oscillations. An extension of this framework, the *Wendling–Chauvel model* (39–41), incorporates dual inhibitory systems mediated by GABA_A and GABA_B receptors, enabling a more accurate representation of epileptiform activity anchored in the physiology of hippocampal CA1 and temporal cortex. These models reproduce realistic oscillatory frequencies and waveforms, include physiologically interpretable parameters, and are well-suited to study how biological perturbations, such as pharmacological manipulations or lesions, affect network activity.

Neural mean-field models (NMFMs) represent a specific subclass of neural mass models situated toward the biophysical end of the spectrum. They are derived analytically from networks of spiking neurons. Typically, mean-field derivations of NMFMs involve defining a set of state variables which represent the average firing rate and average membrane potential of each neuronal population within the model, and constructing a system of ordinary differential equations (ODEs) that describe how these state variables evolve over time.

On the other hand the phenomenological neural mass models focus on reproducing collective dynamics. A prominent example is the *Epileptor model*, which captures seizure onset, offset, and temporal structure using nonlinear differential equations with fast and slow subsystems, without modeling EPSPs, IPSPs, or ion channels. Another simple example is represented by the *Stuart–Landau oscillator*, which provides a minimal description of oscillatory neural dynamics. This model is derived from the normal form of a Hopf bifurcation, a canonical mechanism through which stable oscillations emerge when a system crosses a critical threshold.

Modeling at the Macroscale

Different from microscale models, made of neurons and synapses, and from mesoscale models that capture the dynamics of local populations, macroscale modeling focuses on the interaction between entire brain regions and the emergent global dynamics resulting from their coordinated activity. Macroscale models are generally virtual brain models built from anatomo-functional reconstructions (18,42–45).

At this level, the brain is typically represented as a network of interconnected nodes (functional areas), described by simplified models of neural activity (e.g. neural masses), and the edges reflect the anatomical connectivity derived from diffusion MRI or tractography. This network structure captures how large-scale interactions shape the brain's functional organization. Hence, macroscale modeling plays a crucial role in bridging structure and function. In particular, they enable the investigation of how structural connectivity constrains functional dynamics, producing rich spatiotemporal patterns observable in EEG, MEG, and fMRI.

Importantly, these models can offer insight into both healthy and pathological network states. For example, in MS, where pathology predominantly affects signal conduction delays along white matter pathways, whole-brain models composed of networks of Stuart–Landau oscillators are able to reproduce characteristic large-scale electrophysiological alterations, such as the slowing of alpha rhythms. By adjusting a small set of control parameters, these models can capture essential dynamical phenomena providing a computationally efficient framework to investigate how structural disconnection impacts global brain dynamics in this pathology.

A prominent example of a macroscale modeling platform is The Virtual Brain (TVB) (42), which integrates empirical structural connectivity with neural mass models at each node to simulate whole-brain dynamics. By incorporating subject-specific data, TVB enables the creation of a digital brain twin, a personalized computational replica of an individual's brain that reflects both its structural and functional organization. This approach plays a key role in advancing personalized computational neuroscience by allowing researchers to simulate how individual differences in connectivity and dynamics give rise to specific patterns of brain activity. In epilepsy, for example, TVB-based digital twins have demonstrated strong predictive power, enabling the identification of epileptogenic zones and supporting the

assessment of potential surgical targets for resection (46–48). This patient-specific modeling framework opens new avenues for precision diagnostics, prognosis, and treatment planning.

Choosing the Right Level of Abstraction

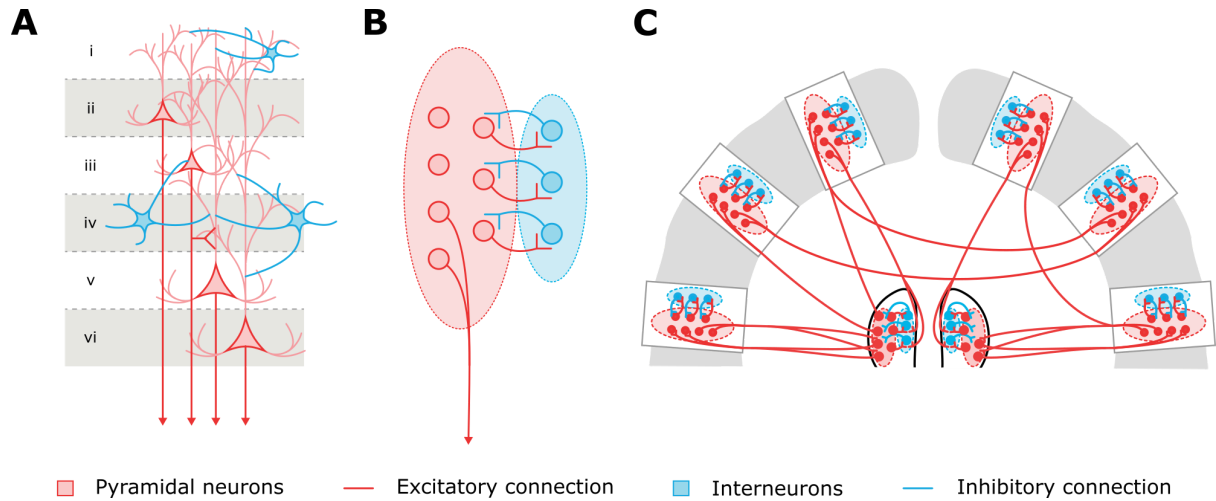


Figure 3. Schema of common models in computational neuroscience. (a) Spiking neural networks are constructed by coupling numerous instances of single-cell models (e.g. Pyramidal neurons, interneurons, and excitatory interneurons) together. (b) Neural mass models (via mean-field approximations), are derived by mathematical reduction of the majority of neurobiological characteristics of a biological neural network (e.g. cell type, internal/external connections, and anatomical organization). (c) Whole-brain model of coupled neural mass models connected via structural connectivity. Figure adapted from Breakspear et al. (20).

In computational neuroscience, there is no single “best” model but only one that best fits a given scientific question. The decision about which model to use depends on the scale of the question. Modeling the brain requires choosing the appropriate level of abstraction from microscopic biophysical descriptions to macroscopic network-level formulations. Each level offers unique insights, but also specific limitations, and the key is to align the model’s complexity with the phenomenon under investigation.

At the microscale, biophysical models such as the Hodgkin–Huxley or multi-compartmental neuron models are essential when the goal is to understand how ionic mechanisms, channel kinetics, or dendritic morphology shape neuronal excitability and synaptic integration. These models provide detailed mechanistic insight but are computationally expensive and difficult to scale up. Simplified phenomenological formulations, such as leaky or quadratic integrate-and-fire neurons, sacrifice biophysical realism for efficiency, making them suitable for studying how single-neuron properties contribute to network computations. At the mesoscale, the focus shifts to the collective behavior of local populations. Neural mass models describe the average activity of large neuronal ensembles in terms of a few

macroscopic variables, such as mean membrane potential or firing rate. These formulations are particularly useful when investigating how excitatory–inhibitory balance, synaptic time constants, or coupling strengths shape oscillatory rhythms and local synchronization. Finally, at the macroscale, models aim to capture the coordinated dynamics emerging from interactions among entire brain regions.

These modeling approaches should not be viewed as distinct categories but as points along a continuous hierarchy. This adaptability across scales makes computational modeling a powerful bridge between theory and experiment. By selecting the right level of abstraction, researchers can balance biological realism and computational tractability, ensuring that each model captures the essential mechanisms relevant to the question at hand, from molecules to cognition, and from single neurons to the dynamics of the whole brain.

Forward and inverse modeling

Following selection of suitable dynamical models –which can robustly represent neural activity– across spatiotemporal brain scales, we encounter an issue of equal importance: how can we establish a reliable link between empirical observations, and model parameters? Put more formally, we require a framework which enables us to infer latent state variables (unobservable neural processes represented via the model) from observables (neural activity at the chosen scale). Within the context of this framework, going from model parameters to simulated–observables is known as the forward problem, whereas trying to map experimental observations to model parameters is known as the inverse problem.

Put another way, a forward model predicts the effects based on knowledge of the causes (via the likelihood distribution), whereas an inverse model elucidates the causes starting from the observed effects (via the posterior distribution). Formally, given a model $F(p)$ and its parameters p , it is possible to predict an observable as $d_{obs} = F(p)$. Conversely, one can determine the parameters p from the observables d_{obs} : $p = F^{-1}(d_{obs})$ (49).

In the context of neural systems, forward modeling involves simulation of neural activity based on known physiological processes and characteristics (i.e. parameters) to generate in-silico (i.e. synthetic) brain signals that can be compared with empirical data. Inverse modeling, by contrast, aims to uncover the hidden parameters or mechanisms that best

explain observed data, thereby grounding the model in biological reality. Modeling can proceed in either direction: from elementary causes to collective functions (bottom-up, direct problem) or by inferring hidden causes from observables (top-down, inverse problem).

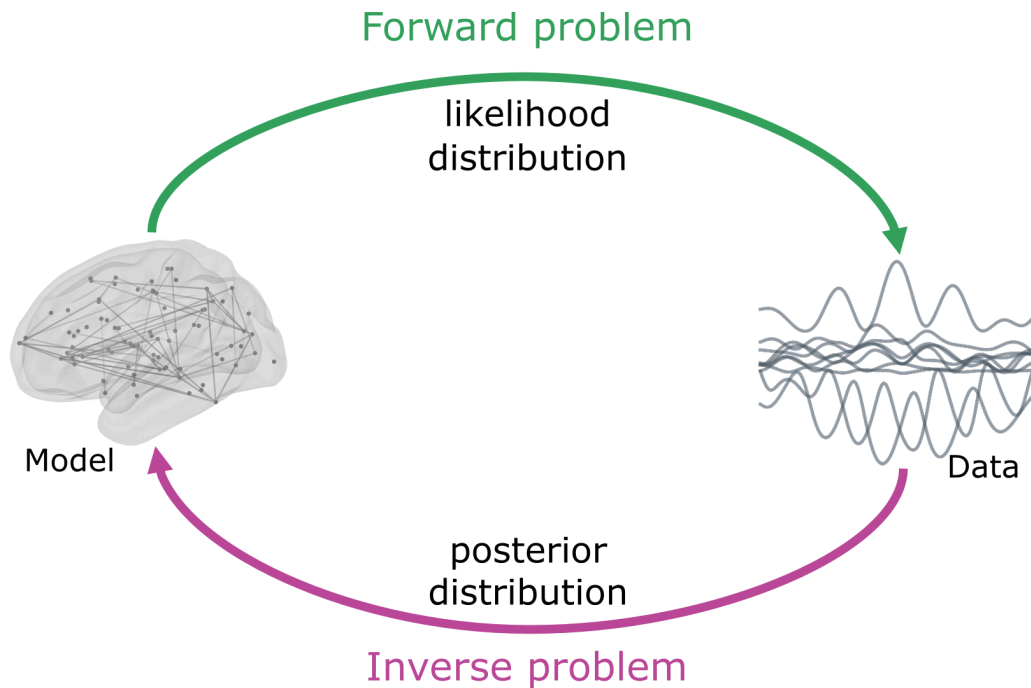


Figure 4. Forward and inverse problems. Simulations of a generative --forward-- model of whole-brain dynamics can be used to infer biologically-relevant parameters from empirical observations, via solving the inverse problem. The likelihood distribution is defined as the probability of observed data given a model parameter. In contrast, the posterior distribution represents our updated beliefs, or the probability of inferred parameters given observed data.

In many biological systems, multiple distinct parameter configurations can produce the same observable behavior. This inherent ‘degeneracy’ means that neither improved optimization, nor larger datasets can guarantee recovery of a single, true set of underlying causes. . Hence, the physiological processes driving recorded activity are often not directly accessible. Model-based inference provides a principled approach to address this challenge by constructing mechanistic models that reflect both the data-generating process and the structure embedded in the observations (50). This approach is particularly valuable in clinical and pathological contexts, where uncovering latent mechanisms is critical for developing a more granular understanding and treatment of neuropathologies such as epilepsy (51–53), and Alzheimer’s disease (54,55).

MCMC (Markov Chain Monte Carlo) is among the standard techniques for carrying out Bayesian inference (56). Markov Chain Monte Carlo (MCMC) methods generate sequences of parameter states where each new proposal depends on the current one, guiding the chain

toward regions of higher posterior probability while still allowing stochastic exploration. This framework enables principled sampling from complex parameter distributions, but gradient-free implementations often exhibit slow convergence and struggle with the highly complex posterior distributions common in modern neural models. Hamiltonian Monte Carlo (HMC) addresses many of these challenges by incorporating gradient information, improving efficiency while retaining the theoretical strengths of the MCMC paradigm. And while HMC provides asymptotically exact posterior samples, its practical use can be limited; Simulating Hamiltonian dynamics at every step becomes computationally expensive for large-scale neural models (i.e. biologically-plausible spiking neural networks). In addition, any new data or preprocessing change requires rerunning the full inference procedure, a limitation which is compounded by the sensitivity of this method to fine-grained fluctuations in the data.

To overcome these limitations, *Simulation-Based Inference (SBI)* has emerged as a powerful alternative (57,58). The core idea is simple: sample parameters from prior distributions, generate synthetic data through forward simulations, and train a neural network to learn –a one-to-one and thus invertible– mapping between empirical data and model parameters. Once trained, this network, given unseen empirical observations, can infer posterior distribution of parameters in an efficient, scalable, and amortized manner. In short, the neural network underlying SBI allows one to learn how observed data –or features computed thereof– are best explained in terms of model parameters. Once the network is trained, inference becomes extremely fast, as the learned weights from said invertible mapping allows one to quickly estimate hidden parameters, bypassing the need for re-running numerous simulations for each observable data point. Furthermore, this makes SBI particularly well-suited for inferring parameters from complex, high-dimensional models such as those representing a neural subpopulation via activity of thousands of single-neurons. This methodology has already been successfully applied across several neurological conditions, including epilepsy and multiple sclerosis (14,59), demonstrating its strong clinical potential. In particular, SBI represents a major step forward in overcoming the cyclic and time-consuming nature of traditional probabilistic inference in neuroscience, enabling more efficient and empirically informed parameter estimation.

2. A realistic computational model for the formation of a Place Cell

This chapter addresses the development of a biophysical multicompartmental model of a hippocampal CA1 pyramidal neuron, designed to self-organize its synaptic inputs and acquire place cell properties, thereby reproducing the stable and location-specific firing patterns observed experimentally. It provides a mechanistic framework for understanding how dendritic integration and synaptic plasticity enable a single neuron to encode spatial cues, offering critical insights into cellular processes that may be disrupted in Alzheimer's disease.

2.1 Anatomical and Neurophysiological Organization of the Hippocampus

A rigorous anatomical and neurophysiological characterization of the target structure is a fundamental prerequisite for model development, particularly when the objective is to implement a biophysically plausible microscale model.

The hippocampus is a brain area located inside the medial temporal lobe and it is part of the hippocampal formation, a region of the telencephalon consisting of the hippocampus, subicular cortices, entorhinal cortex, and dentate gyrus. The hippocampal formation, together with the cingulate gyrus, parahippocampal gyrus, and surrounding cortices, forms the limbic lobe.

The hippocampus plays a primary role in the formation of explicit memories, in learning processes, in the transformation of short-term memory into long-term memory, and in the formation of fundamental maps for spatial navigation.

Important information regarding the functions of the hippocampus was obtained thanks to Henry Gustav Molaison, better known as patient H.M (60). Due to violent epileptic seizures, patient H.M. was unable to live a normal life; Therefore, he decided to undergo bilateral removal of the central portion of the temporal lobes (hippocampus and surrounding cortex) in order to resolve the seizures. After the operation, although Henry had been freed from his violent epileptic crises, he began to suffer from anterograde amnesia: he could remember only experiences prior to the surgical intervention but was no longer able to form new

memories. H.M., however, could acquire and maintain new procedural memories, a sign that the hippocampus was important only for certain types of memory, particularly explicit (episodic and semantic) memory. It was later found that Alzheimer's disease, whose first symptoms are amnesia and disorientation, also derives from hippocampal damage.

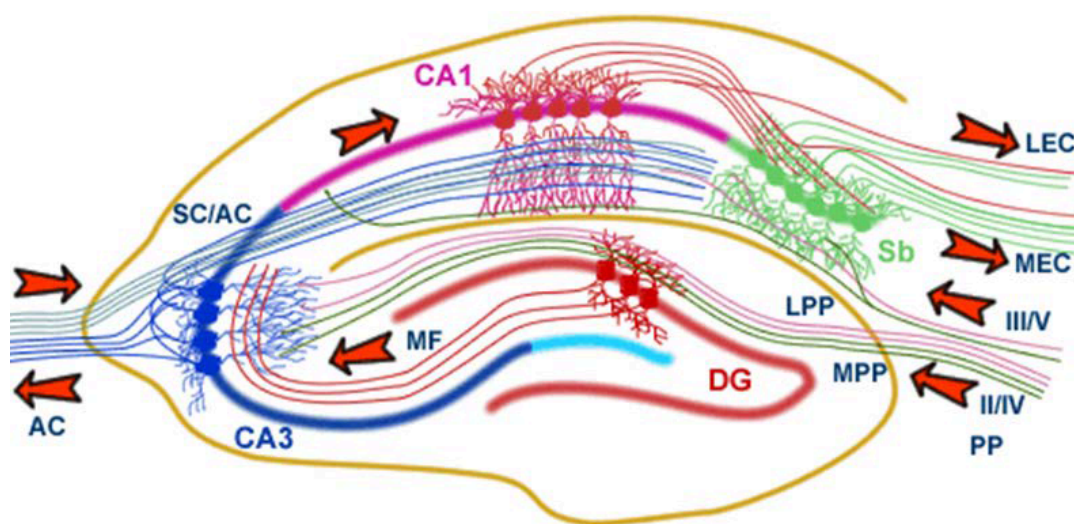


Figure 5. Schematic representation of the main hippocampal circuit, showing the neuronal populations of the dentate gyrus (DG), CA3, and CA1 regions, and their principal connections. The diagram includes the mossy fibers (MF), Schaffer collateral/associational-commissural (SC/AC) pathways, and the lateral and medial perforant paths (LPP and MPP) originating respectively from the lateral entorhinal cortex (LEC) and the medial entorhinal cortex (MEC).

The neocortex, septum, contralateral hippocampus, and modulatory inputs from the reticular formation project to the hippocampus either through the entorhinal cortex or via the fornix. Through the entorhinal cortex, the hippocampus establishes a bidirectional communication with the cortex, especially with associative areas and primary sensory cortex. Information originating from these cortical areas converges onto the entorhinal area and then reaches the hippocampus. After processing the information, the hippocampus relays it back to the entorhinal area and subsequently to the neocortex. Two main pathways originate from the entorhinal cortex: the perforant pathway and the alvear pathway. The first consists of fibers that travel along the subiculum and, after crossing the base of the hippocampal sulcus, end in the dentate gyrus, which in turn projects back to the hippocampus. The second is formed by fibers that reach different hippocampal regions by passing through the alveus, which constitutes a thin layer of white matter. Through the fornix, afferent fibers originate from the contralateral hippocampus and the septum, cholinergic afferents from the thalamus and hypothalamus, dopaminergic afferents from mesolimbic structures such as the ventral tegmental area (VTA), substantia nigra (62), and serotonergic afferents from the raphe nuclei. Dopaminergic afferents provide a neuromodulatory signal that regulates the consolidation of hippocampus-dependent memory for new events, both in rodents and in humans (63). Regarding efferent projections, the axons originating from the hippocampal formation form the alveus; these fibers continue into the fimbria and then converge into the fornix. The hippocampus projects to the subiculum, which in turn is connected with the neocortex, amygdala, entorhinal cortex, and striatum. Moreover, there is a circuit originating from the subiculum of the hippocampal formation. This circuit, known as the Papez circuit, projects through the fornix to the mammillary bodies of the hypothalamus. From the mammillary bodies, through the mammillothalamic tract (often known as Vicq d'Azir tract), reaches the anterior nuclei of the thalamus, then the cingulate gyrus, continues through the entorhinal cortex, and finally returns to the hippocampal formation (64). This circuit plays a key role in the regulation of emotions and memory. In general, the hippocampus–amygdala circuit, which passes through the nucleus accumbens, is involved during memorization processes dependent on emotional state. The latter half of said circuit communicates with both cortical sensory areas and deep brain structures, while the former half is connected with sensory areas, thalamus, hippocampal gyrus, and other associative areas, as previously mentioned. In instances where processing of associative memories involves information with strong emotional content, the amygdala acts as an intermediary for cortical areas engaged in emotion

regulation, such as the frontal cortex. This region -in conjunction with the hypothalamus- conveys information regarding internal homeostasis.

2.2 Place Cells, Grid Cells, Head Direction Cells and Speed Cells

Edward C. Tolman, an American psychologist and professor of psychology at University of California, Berkeley, was the first to introduce the concept of *cognitive maps* (65). Through a series of behavioral studies on mice, Tolman demonstrated that these animals, when moving from one point to another within an environment, were capable of taking both shortcuts and detours. In his experiments, mice were trained to follow a specific trajectory leading to a reward (Figure 6a). After the training period, they were presented with several alternative routes that had not been available during the learning phase (Figure 6b). Remarkably, Tolman observed that the mice often selected a previously inaccessible shortcut rather than simply repeating the familiar path, suggesting the formation of an internal spatial representation of the environment.

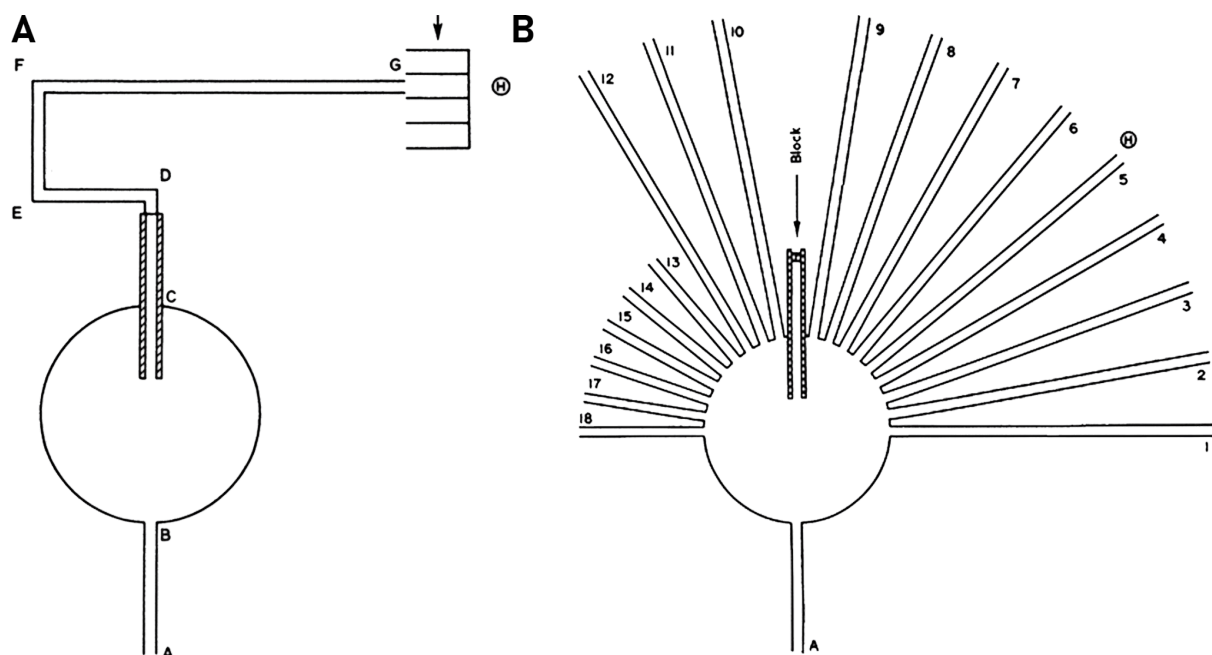


Figure 6. Experimental setup of Tolman's studies in spatial learning. A. Maze apparatus outline of the preliminary training. B. Maze apparatus outline of the test sessions. Taken from (65).

Decades later, this theoretical insight found direct neurophysiological support with the discovery of Place cells (PCs) by John O'Keefe in 1970 (66). By recording the electrical activity of single hippocampal neurons through microelectrodes, O'Keefe observed that specific CA1 pyramidal neurons increased their firing rates when a rat occupied particular

locations in a confined arena. This spatially selective activity defined the *place field* of each neuron and provided the first physiological evidence for Tolman's cognitive map hypothesis.

Place Cells are now recognized as a key component of the neural system that encodes spatial representations. They work in concert with other specialized cell types, such as head direction cells (67–69), border cells (70,71), grid cells (72), and speed cells (73) to support efficient spatial navigation and orientation. Their presence has been documented in several mammalian species, including bats and primates (74–79), indicating that the neural mechanisms underlying spatial cognition are evolutionarily conserved.

Despite the extensive body of evidence, the cellular and synaptic mechanisms by which a hippocampal pyramidal neuron becomes a Place Cell remain incompletely understood. In the CA1 region of the hippocampus, experimental findings suggest that the convergence of inputs from the entorhinal cortex and the Schaffer collaterals can induce PC formation (80) through a finely tuned interaction between spatially distinct and temporally coordinated signals. However, because the dynamics of this integration are particularly challenging to study experimentally *in vivo*, a more detailed mechanistic framework is required to elucidate both the fundamental processes underlying PC emergence and the cognitive functions that depend on their normal operation.

For these reasons, a realistic computational model of Place cell formation was developed and is presented here. The results indicate how, to what extent, and under which conditions dendritic integration and synaptic plasticity processes can transform a CA1 pyramidal neuron into a Place Cell.

2.3 Model Implementation

The implementation of the model and its operation are schematically illustrated in Figure 7.

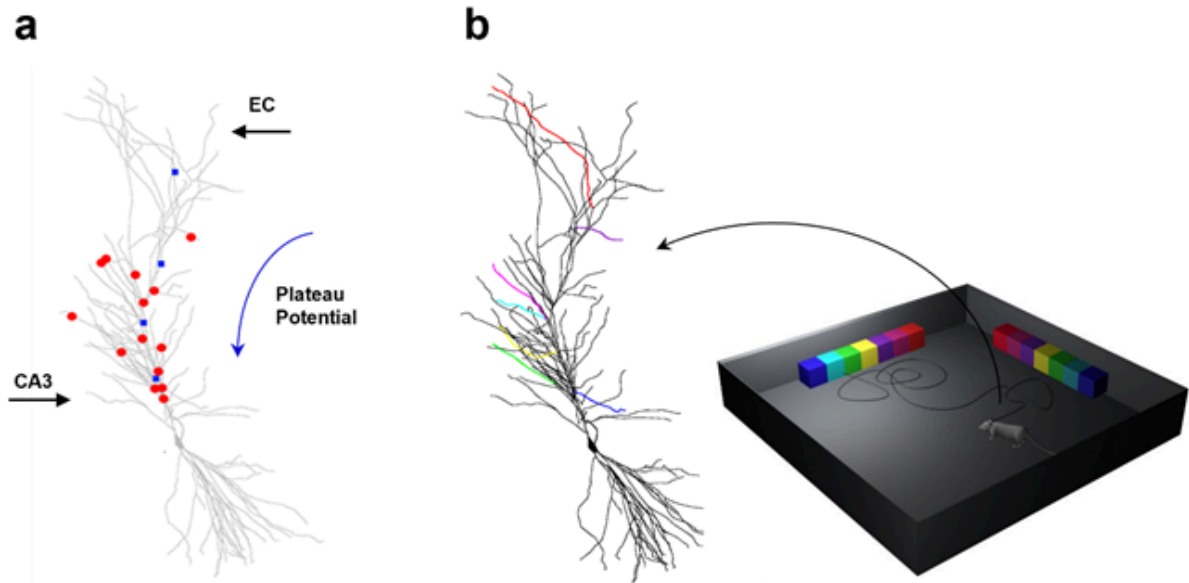


Figure 7. Multicompartmental model leads to dendritic encoding of spatial information and PC formation. (a) Input from the proximal Shaffer Collateral (CA3) together with a distal input from the entorhinal cortex (EC) generates a plateau potential, whose propagation is annotated by the blue arrow. Red circles represent SC synapses and blue squares are the locations of input current that were used to simulate the plateau potential propagation. (b) Different oblique dendrites encoded the different colored cubes (rainbow cue). All simulations were implemented based on this CA1 neuron and specific virtual environment. The spot light indicates the virtual mouse's current visual field.

All simulations were conducted using the NEURON simulation environment (v7.5) (Carnevale and Hines, 2006). This software is particularly well-suited for simulating neurons with complex morphology and biophysical properties, as it allows the definition of individual properties for each isopotential compartment.

The CA1 neuron was modeled with nonlinear differential equations following the Hodgkin–Huxley model (28). The neuron morphology and channel kinetics correspond to those described and systematically validated in previous studies on CA1 pyramidal neurons (81). The morphology is compounded of a soma, an axon, 74 oblique dendrites, 58 basal dendrites, and 67 membrane sections forming the main apical trunk and distal tuft. We implemented Na^+ and K_{DR} currents, two K_{A} currents, one for the proximal and one for the distal dendrites, an I_h current, and a M-type potassium current, K_{M} (inserted in the soma and in the axon). The K_{A} and I_h peak conductance increased linearly with distance from the soma (82–84).

The model was inspired by experimental findings showing that Place cells can emerge from the precise conjunction of two dendritic signals (80). Two spatially segregated excitatory

inputs converge onto CA1 pyramidal neurons, representing highly preprocessed sensory and contextual signals:

1. *The Perforant pathway* which originates in the entorhinal cortex (EC) and innervates the distal apical dendrites.
2. *Schaffer collaterals*, arising from CA3 and projecting onto proximal oblique dendrites.

Experimental work has suggested that the temporal coordination of these two inputs during environmental exploration and reward search constitutes a fundamental mechanism underlying place cell formation (80).

In the model, CA3 inputs (schematically shown as red circles in Figure 7a) were implemented as excitatory synapses containing both AMPA and NMDA components, following the approach of Gasparini et al. (84). The AMPA current was modeled with a double-exponential conductance profile, characterized by rise and decay time constants of 0.5 ms and 1 ms, respectively, and a reversal potential of 0 mV. The NMDA component followed a kinetic scheme fitted to experimental data (85), assuming an extracellular Mg^{2+} concentration of 1 mM and a reversal potential of 0 mV. These synapses were placed on oblique dendrites, consistent with evidence that the majority of excitatory inputs to CA1 neurons target this compartment (86). To reduce artifacts related to dendritic morphology, the peak conductance in each oblique dendrite was individually tuned to lie just below the spiking threshold at background activity levels. As reported in prior studies (87), this configuration yielded dendritic depolarizations that increased with distance from the soma while producing a uniform peak somatic depolarization. Figure 8 illustrates representative EPSPs recorded in four different oblique dendrites, with the inset showing the average somatic response (variance shaded in light red).

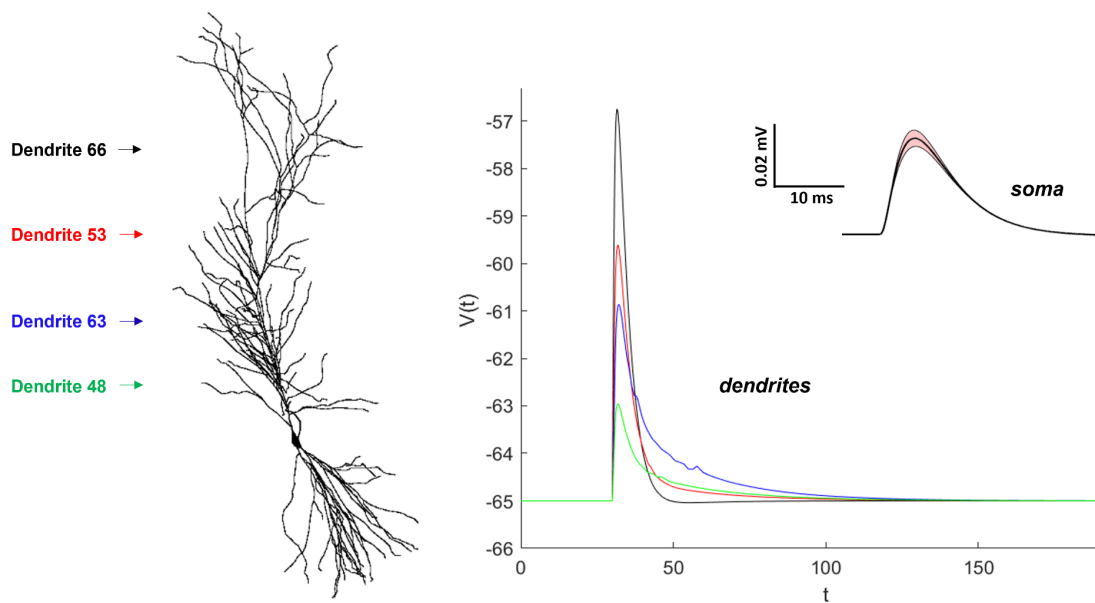


Figure 8. Four increasingly further from the soma oblique dendrites exhibit characteristic EPSPs. The inset displays subsequent depolarization (averaged with variance equal to the light red area) of the soma after individual synaptic activation.

The effect of EC activation was empirically reproduced by sequentially activating four electrode sites along the apical trunk (indicated as blue squares in Figure 7a). Stimulation began at the most distal site to mimic a strong EC input and progressed toward the soma at 500 ms intervals, with each current injection lasting 200 ms. This protocol reproduced the forward propagation of a dendritic plateau potential without explicitly modeling the underlying calcium dynamics, which would have been computationally more expensive. As the virtual animal remained within the same spatial location during this plateau, the co-occurrence of presynaptic activation of oblique dendrites (encoding environmental cues) and postsynaptic depolarization created conditions favorable for synaptic potentiation, ultimately leading to the formation of a place cell.

The study then tested whether such a dendritic plateau, propagating toward the soma, could selectively induce plasticity in synapses activated by environmental cues during navigation, thereby generating or remapping a place cell. A schematic representation of this process is presented in Figure 7b. During simulations, a virtual animal explored a square arena containing multiple cues (depicted as colored “rainbow” objects in Figure 7b) along a random trajectory. The animal’s visual field was set at 90°, with resolution decreasing with distance. Depending on its position and head orientation, entire objects or their parts entered the visual

field. The model assumes that distinct features of an object activate separate dendritic branches through CA3 inputs, eliciting local dendritic spikes that can generate somatic action potentials signaling object recognition (81). This is consistent with human studies showing that single hippocampal neurons respond selectively to highly specific visual stimuli such as individual people, landmarks, or objects (75,82,83).

In the model, each object was segmented into distinct parts, and each part was mapped onto a different oblique dendrite. Consequently, different objects activated distinct sets of dendrites according to their feature composition. There is no definitive experimental evidence specifying how many dendrites should be involved in object coding. Previous modeling work (81) suggested that $7 (\pm 2)$ dendrites yield the most effective representation of an object. For this reason, in order to represent two objects, 14 AMPA + NMDA synapses were distributed across 14 oblique dendrites, with each synapse representing the synchronous activation of a group of synapses. This abstraction omits the nonlinear spatiotemporal summation of synaptic inputs but reflects the principal mechanisms of dendritic integration in CA1 pyramidal neurons.

This modeling strategy was deliberately designed to balance computational efficiency and biophysical realism. Consequently, several mechanisms were implemented in an effective rather than fully detailed manner. In particular, all processes underlying local dendritic spiking were incorporated into computationally efficient AMPA and NMDA synapses. Even in the absence of explicit calcium dynamics, the model's dendritic integration is substantially more realistic than traditional point-neuron approaches typically used in large-scale network modeling.

Under baseline conditions, synapses not associated with visual features were activated stochastically (Poisson process) at 3 Hz, corresponding to theta-range rhythms. When known features (object parts) entered the visual field, their associated synapses (colored dendrites in Figure 7b) were driven at high-gamma frequency (~ 80 Hz). Distinct object parts activated separate dendritic branches, generating local dendritic action potentials and, in turn, somatic spiking (81–86). These synaptic activation rates were chosen in line with experimental and theoretical evidence indicating that working memory is coordinated by theta–gamma oscillatory dynamics (87). Moreover, computational studies based on experimental data have shown that periodic theta–gamma–coordinated reactivation (or replay) supports working

memory and that gamma activity contributes critically to attention, memory performance (88), and other cognitive functions (89).

Synaptic plasticity

Synaptic weights were modified according to a Spike Timing–Dependent Plasticity (STDP) rule previously employed in earlier studies (90), in agreement with experimental observations in CA1 pyramidal neurons (91). This rule determines whether long-term potentiation (LTP) or long-term depression (LTD) occurs, depending on the temporal relationship between pre- and postsynaptic activations. In particular, the induction of LTP or LTD, corresponding to changes in peak synaptic conductance, is governed by the correlation between presynaptic (t_{pre}) and postsynaptic (t_{post}) spike times. For $(t_{post} - t_{pre}) > 0$, LTP is induced, whereas for $(t_{post} - t_{pre}) < 0$, LTD occurs. If the local synaptic signal is insufficient to trigger a dendritic spike, no t_{post} is generated, and consequently, no change in synaptic weight takes place. A dendritic spike can emerge either when a single synapse is strong enough to elicit it or when surrounding inputs produce a sufficient depolarization to summate with the local signal. More specifically, the peak synaptic conductance of each synapse was updated at any occurrence of a pre- or post-synaptic spike time (t_{pre} , t_{post} , respectively) as:

$$g_{peak}(t+dt) = g_{peak}^0 + A(t)$$

$$A(t+dt) = A(t) * \left(1 - d * \frac{e^{-\frac{-(t_{post}-t_{pre})-M)^2}{2V^2}}}{V\sqrt{2\pi}} \right)$$

for $(t_{post} - t_{pre}) < 0$ and

$$A(t+dt) = A(t) * \left(g_{peak}^{max} - g_{peak}^0 - A(t) \right) * p * e^{\frac{-(t_{post}-t_{pre})}{\tau}}$$

for $(t_{post} - t_{pre}) > 0$

The parameters $M = -24$, $V = 6.32$, $\tau = 2$, $d = 0.3$, and $p = 1$ were selected to match experimental data of Nishiyama et al. (91). Here, g_{peak}^0 represents the initial peak conductance, while g_{peak}^{max} corresponds to its maximal value. The potentiation factor $A \geq 0$ represents the degree of synaptic strengthening. Dendritic spike times were defined as the instants when the local membrane potential exceeded the threshold of -10 mV.

2.4 Results

As previously outlined, one of the fundamental mechanisms involved in the association of the two major excitatory inputs converging onto a CA1 pyramidal neuron relies on the generation of a depolarizing plateau potential in the distal apical dendritic tree, which then propagates toward the soma. In the model, this phenomenon was reproduced by the activation of electrodes distributed along the main apical trunk (see “Model implementation”).

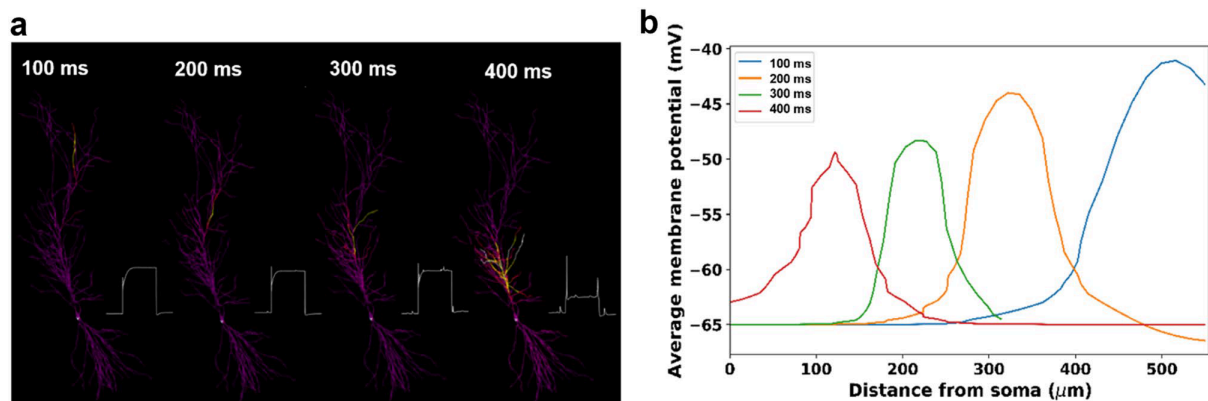


Figure 9. Plateau potential propagation towards the soma. (a) The membrane depolarization is displayed at four sequential time points. The higher depolarized parts are illustrated with white/yellow; The insets show the corresponding membrane voltage recordings occurring at locations of maximum depolarization for each snapshot. (b) Correspondent recordings of the average membrane potential with respect to the distance from the soma.

The activation of these current injections produced a depolarizing wave that progressively involved dendritic regions closer to the soma, as suggested by experimental observations (80). This process is shown in Figure 9a, which presents four representative snapshots from a simulation where four electrodes were activated without any background synaptic activity. To better illustrate the propagation of the signal, Figure 9b depicts the average membrane potential as a function of distance from the soma, computed at different time points during the simulation. This analysis highlights the underlying dynamics of the process, which, as further discussed below, plays a central role in the formation of Place Cells.

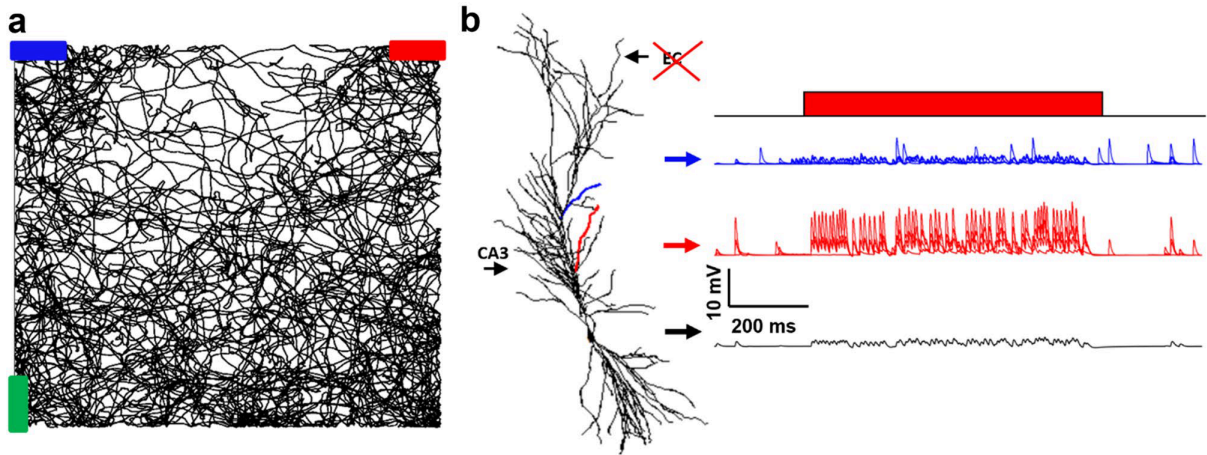


Figure 10. Somatic spiking in the model is prevented without the plateau potential. (a) Random trajectory exhibited by a virtual mouse during a simulation. (b) Just from the CA3 input no plateau potential is generated; thus, as the virtual mouse looks at the red bar, the membrane potential for the blue dendrite, the red dendrite and the soma is measured.

As a first step, a simulation in which a virtual mouse explored an environment containing three different objects (colored bars in Figure 10a) in the absence of the plateau potential was performed. As shown in Fig.10a, while the mouse moved within the arena, a black line traced its random trajectory during the simulation. The recordings shown in Figure 10b display the membrane potential recorded at the soma (black trace) and at two dendritic locations (red and blue traces), corresponding to dendritic compartments targeted by synapses that become active when a red or blue object is present. Before the red object entered the animal's visual field (red bar in Figure 10b), activity in both dendrites was essentially random, showing slow theta-frequency fluctuations. When the red object became visible, the synapses on the red dendrite (but not on the blue one) were strongly activated in the gamma band. However, this alone was insufficient to trigger dendritic or somatic spikes, and thus to activate STDP.

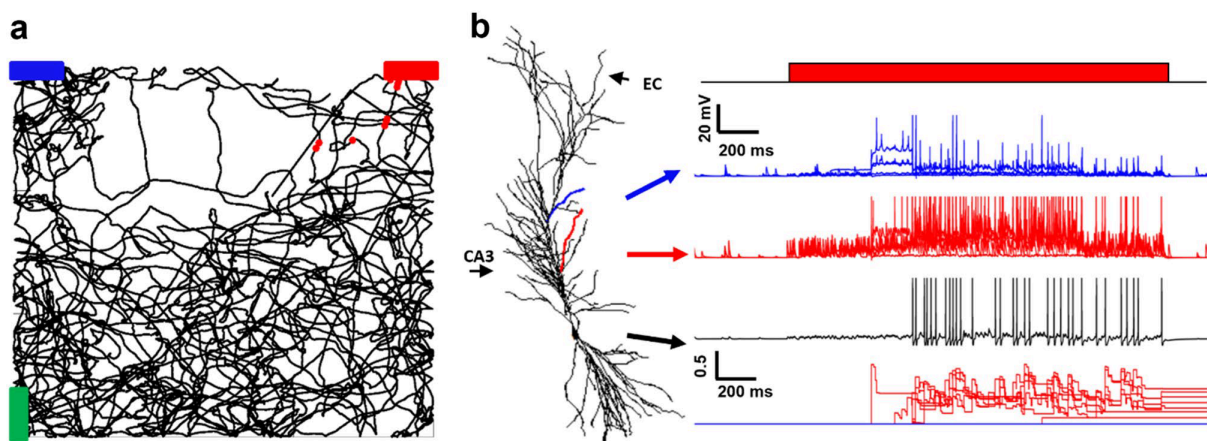


Figure 11. Place cell formation as propagation of the plateau potential induces somatic spiking and STDP. (a) Trajectory of the virtual mouse in the environment. Red dots indicate the positions that triggered neuronal

firing. (b) Similar to Figure 10, but the presence of EC input leads the dendritic spiking to somatic spiking as the mouse faces the red bar. At the bottom, the time evolution of synaptic weights is displayed.

Figure 11a presents the results of the same simulation but with the EC input activated during the period when the red object was in the animal's visual field. Since this input is assumed to convey internal memory-related information and can be modulated by dopaminergic afferents signaling reward, it mimics a contextual or reward-related signal (92). The red dots indicate the positions where the cell fired. While the synapses on the red dendrite were again strongly driven by the red bar, the additional depolarization due to the plateau potential now triggered dendritic spikes, which propagated to the soma (Figure 11b). This burst of activity was sufficient to strengthen the synapses on the red dendrite but not on the blue one (red and blue lines in Figure 11b). Once the object left the visual field of the virtual animal, the synaptic activity on the red dendrite returned to baseline, but with enhanced synaptic weights, marking the formation of a Place Cell.

Importantly, Bittner et al. (93) demonstrated that the time window for pre- and post-synaptic activity in PC-related plasticity can span several seconds, but, for computational efficiency, a shorter timescale was employed. Our approach can therefore be viewed as a compressed-time implementation that allows Place Cell to quickly respond to environmental cues during a simulation, an essential feature for scaling up to large network models. The longer window observed experimentally may be linked to intracellular calcium wave propagation, which occurs on these slower timescales. Future work will investigate how learning rules acting over different timescales, both rapid and slow, affect single-cell and network dynamics.

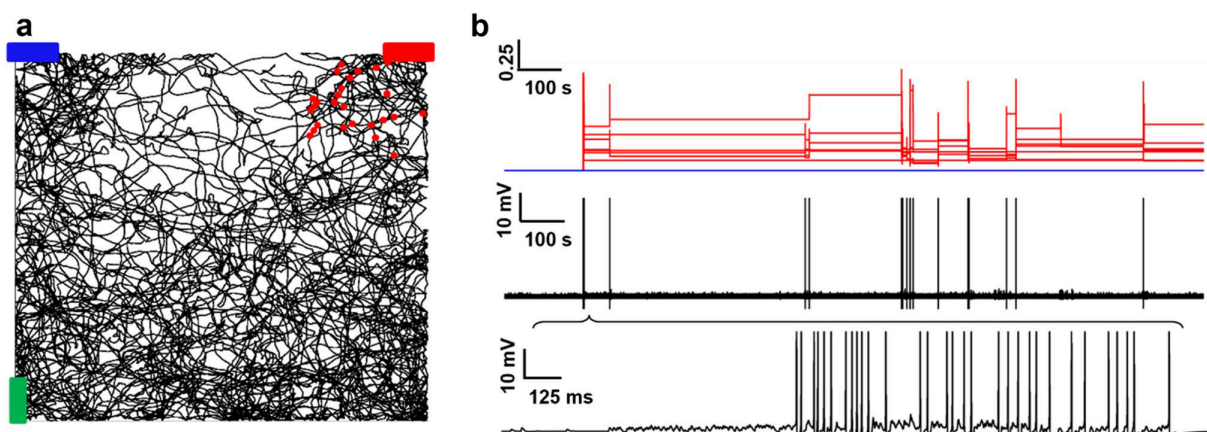


Figure 12. Persistence of place cell activity during longer timescales. (a) Extended trajectory of the virtual mouse reveals the stability of the place cell. (b) Top to bottom: time evolution of synaptic weights; somatic activity; inset of 10 s displaying the somatic membrane potential during the plateau potential activation.

To assess the stability of the Place Cell, the virtual animal was allowed to freely explore the environment for 15 minutes after EC input ended. Figure 12a shows the total trajectory of the animal and the neuron's spike (red dots), while in Figure 12b are shown the evolution of the synaptic weights on the red dendrite and the neural activity recorded at the soma during the all simulation (top two panels), and the neural activity recorded at the soma during the 1-second window of the reward input (bottom panel of Figure 12b). Once formed through the integration of CA3 proximal and EC distal inputs, the Place Cell remained stable over time: even though the weights keep change with time, their strength remained sufficient to elicit somatic spikes whenever the animal revisited the red-bar location, mirroring experimental findings (66,94). Since Place Cell activity in the model is tied to specific environmental cues, its firing naturally correlates with the spatial position of those cues. This is consistent with experiments showing that place-related firing persists even when the environment is rotated (95–97) or cue arrangements are altered (98).

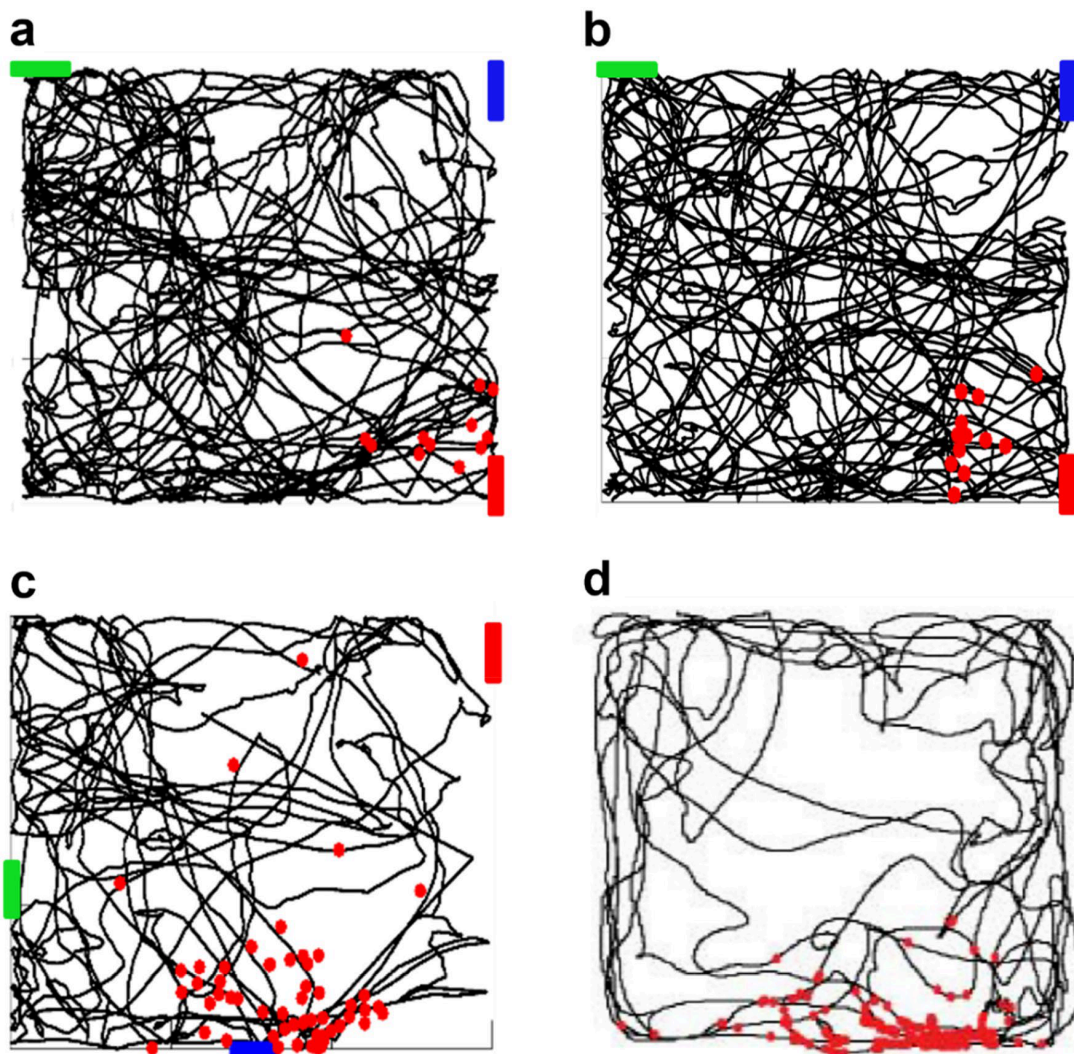
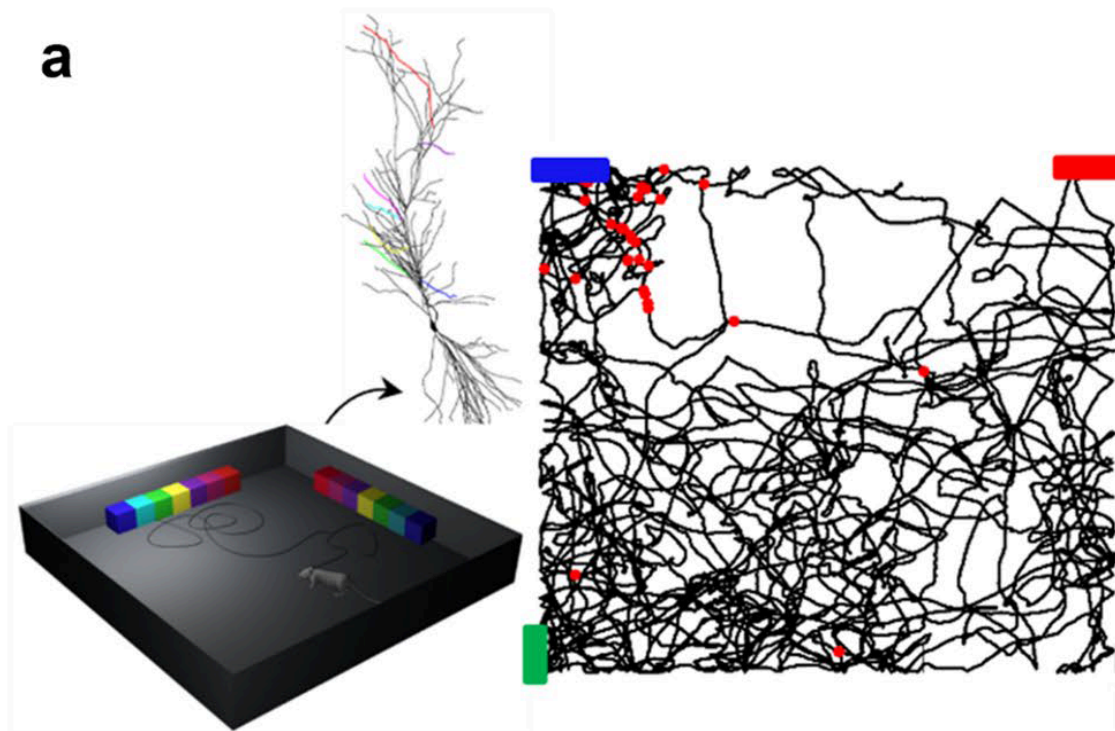


Figure 13. The place cell robustly encodes actual spatial information tested using (a) rotations and (c) different configurations of the virtual environment, (b) multiple trajectories. (d) Experimental results, as shown in Hok. et al. (99), example of a place cell's firing.

To test the flexibility and robustness of the model, additional simulations were conducted. We examined whether a Place Cell could still emerge if: (a) the entire environment was rotated, (b) the animal followed different trajectories, or (c) the object configuration was changed. In all cases, neuron spikes are indicated by red markers in Figure 13. When the arena was rotated (Figure 13a), the Place Cell's activity rotated accordingly. When a new trajectory was used (Figure 13b), the cell was again successfully tuned to the red cue. Finally, Figure 13c shows the result of tuning the cell to a different cue (blue bar), using a distinct dendritic input set. As expected, the Place Field shifted to a different spatial location, as observed in experiments involving distinct contexts (98). This demonstrates both the stability of the mechanism and the neuron's capacity to encode different objects in separate dendritic compartments. A direct comparison with typical experimental recordings (Figure 13d) further highlights this qualitative agreement (99).



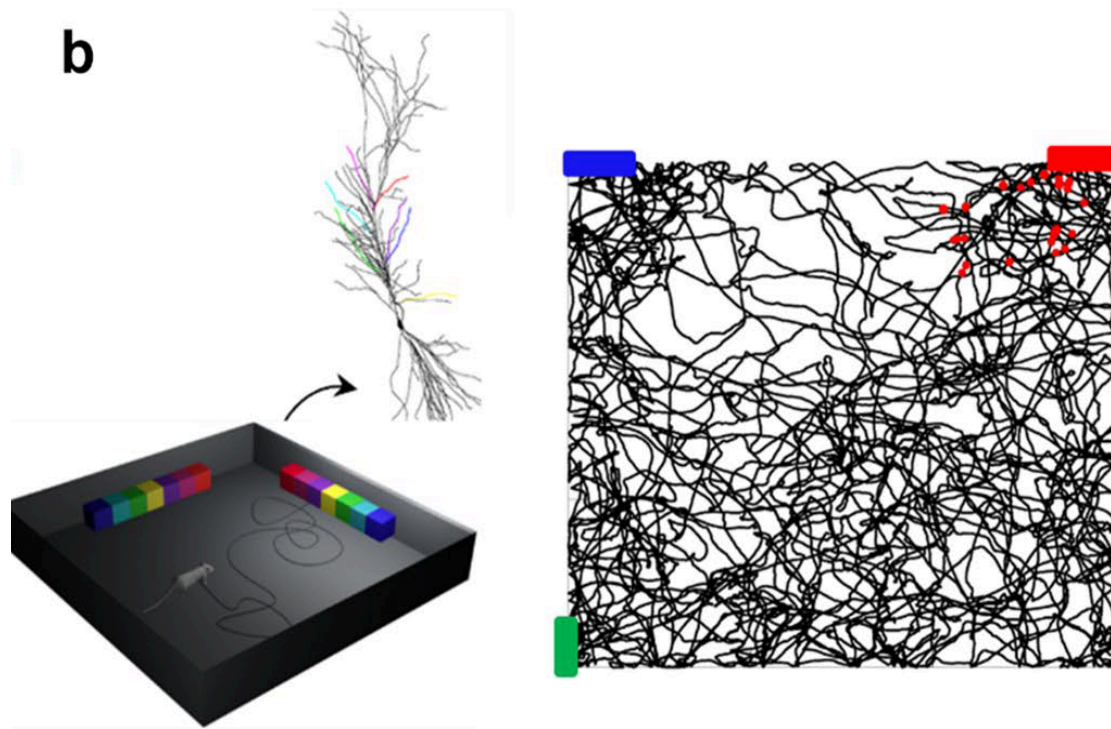


Figure 14. Morphologically identical neurons turn into a place cell encoding for different objects (different simulations). The reward signal propagates when the visual field targets (a) the blue or (b) the red bar. Red dots represent neuronal spiking.

The same principle was explored in Figure 14, where the cell was selectively tuned either to the blue bar (Figure 14a) or to the red bar (Figure 14b), using distinct dendritic inputs for each object (see colored dendrites in Figure 14 a,b). As reported experimentally (98), multiple Place Cells with different place fields can coexist in the same environment. The model therefore supports the possibility that a single neuron can give rise to different Place Cell representations, depending on the dendritic compartment involved.

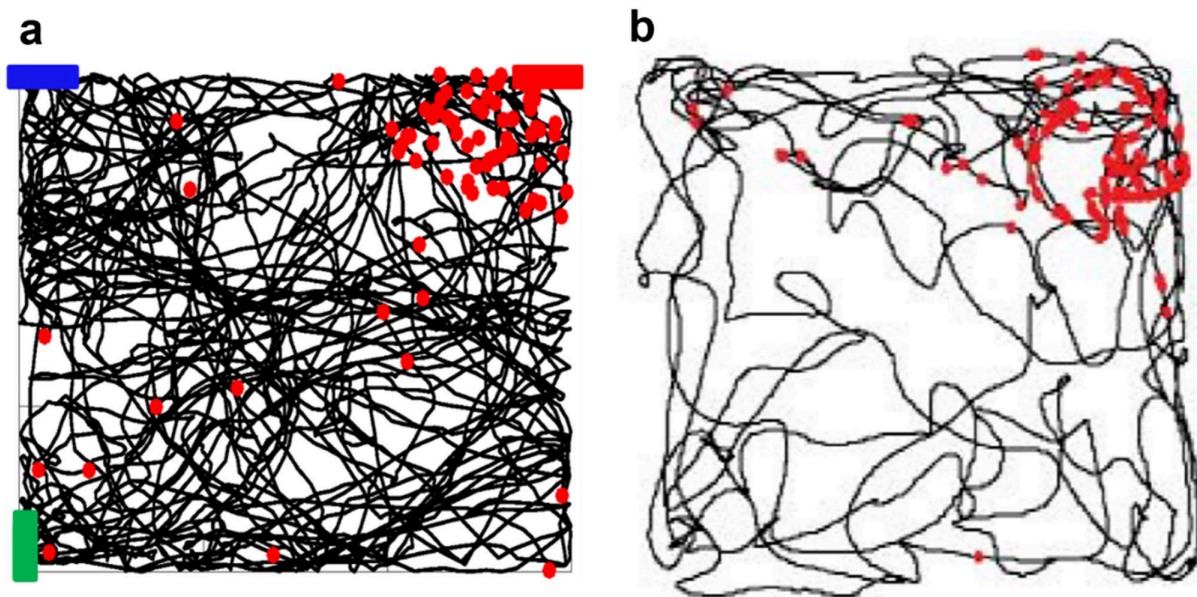


Figure 15. Qualitatively similar results to the experiment were obtained. (a) Trajectories from ten independent simulations post-training period. (b) Typical experimental results obtained in Hok et al. (2012) (99), Figure 4a.

A more extensive demonstration of the model's stability is provided in Figure 15a, which summarizes the results from 10 different random trajectories after training, and compares them with a representative experimental example (Figure 15b) (99).

2.5 Considerations

Spatial navigation is one of the cognitive domains most profoundly affected in Alzheimer's Disease, with alterations in spatial orientation and navigation abilities frequently observed during the course of the disease. A central component of the neural system supporting spatial navigation is the place cell network, which plays a critical role in encoding and integrating spatial information. In this context, developing a biophysically realistic model of place cells provides a valuable framework to explore how cellular and synaptic mechanisms contribute to spatial representation under physiological conditions. Beyond providing insights into the fundamental mechanisms underlying spatial navigation itself, such mechanistic understanding is particularly relevant for Alzheimer's disease, as disruptions in these processes may underlie the observed navigational deficits.

3. Brain Fluidity as a Functional Marker of Tau-Related Neurodegeneration in Alzheimer's Disease

Alzheimer's Disease (AD) is the most common form of dementia and ranks among the foremost neurodegenerative diseases worldwide (100,101). Characterized by a progressive decline in cognitive and functional abilities, AD impairs nearly all aspects of daily living (102–104). Clinically, AD is characterized by progressive memory loss, language difficulties, and spatial disorientation (105–108), followed by impairments in executive function (109–112). As the disease advances, patients often develop apathy, anxiety, and irritability (113–116). These cognitive symptoms reflect a disruption of higher-order brain functions, which rely on the coordinated interaction of multiple brain regions (117).

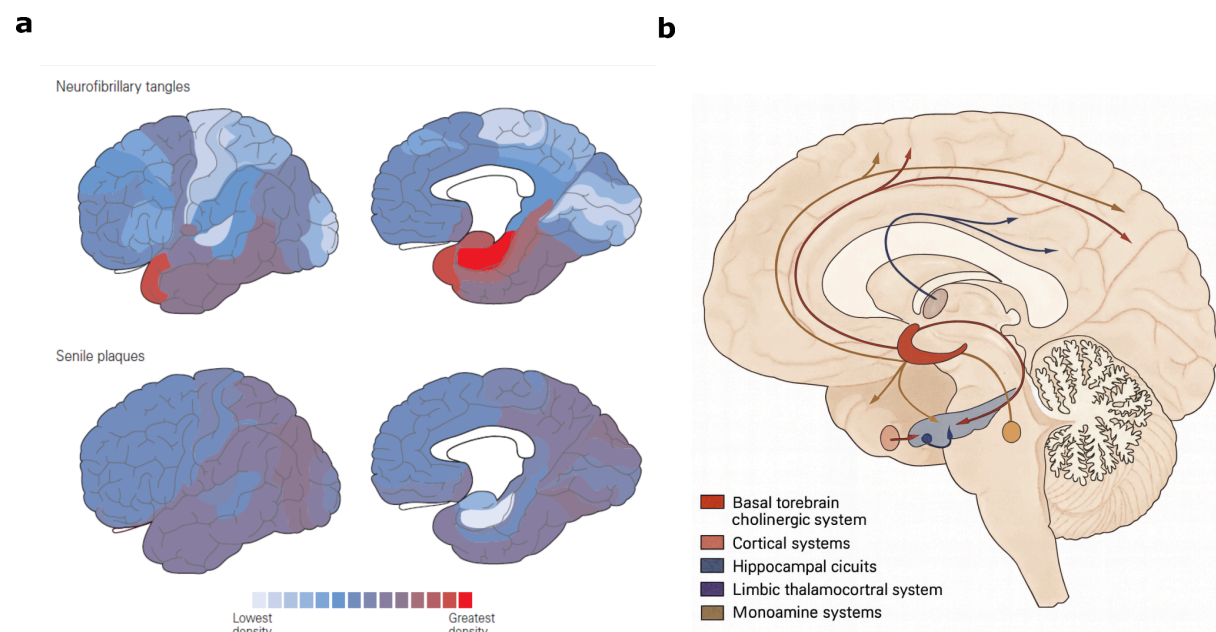


Figure 16. (a) Topographical Distribution and Mean Severity of Neurofibrillary Tangles and Senile Plaques. Lateral and medial views of the cerebral hemisphere display the density of these key pathological hallmarks across 37 of the 39 examined Brodmann areas of the cortex. Note: Subcortical structures such as the amygdala and nucleus basalis of Meynert are not included in this diagram. (b) Vulnerability of Specific Neuronal Systems in Alzheimer's Disease. Morphological and neurochemical analyses reveal that certain, well-defined neuronal systems are selectively susceptible to degeneration. While the figure highlights a key cortical system (entorhinal neurons), it's important to recognize that many neocortical neurons, particularly those within association cortices, are also compromised. The progressive involvement of these distinct brain regions and neural systems directly underlies the clinical signs and symptoms observed in Alzheimer's disease. Taken from Kandel, 2021 (63).

It is characterized by a series of abnormalities in the cytoskeleton, including the deposition of A β peptides and the formation of neurofibrillary tangles, which selectively affect specific

neurons in specific brain regions (118) (Fig.16a). The medial temporal lobe is particularly vulnerable, showing marked atrophy detectable via MRI, FDG-PET, and CSF tau (118–120). The most affected neurons include the pyramidal neurons in the CA1 and CA3 regions of the hippocampus, the pyramidal neurons of the entorhinal cortex, and other circuits in the medial temporal cortex, all of which are considered critical for the memory impairments seen in this disease. Additionally, damage to the association areas of the neocortex contributes to the attention deficits observed in patients. The cholinergic neurons in the nucleus basalis, the medial septal nucleus, and the diagonal band of Broca, which provide the main cholinergic pathways to the neocortex and hippocampus, are also destroyed, leading to reduced levels of acetylcholine and cholinergic markers in their target regions. Behavioral and emotional disturbances in some patients may result from the involvement of the limbic cortex, the amygdala, the thalamus, and several brainstem monoaminergic systems that project to the hippocampal cortex (Fig.16b).

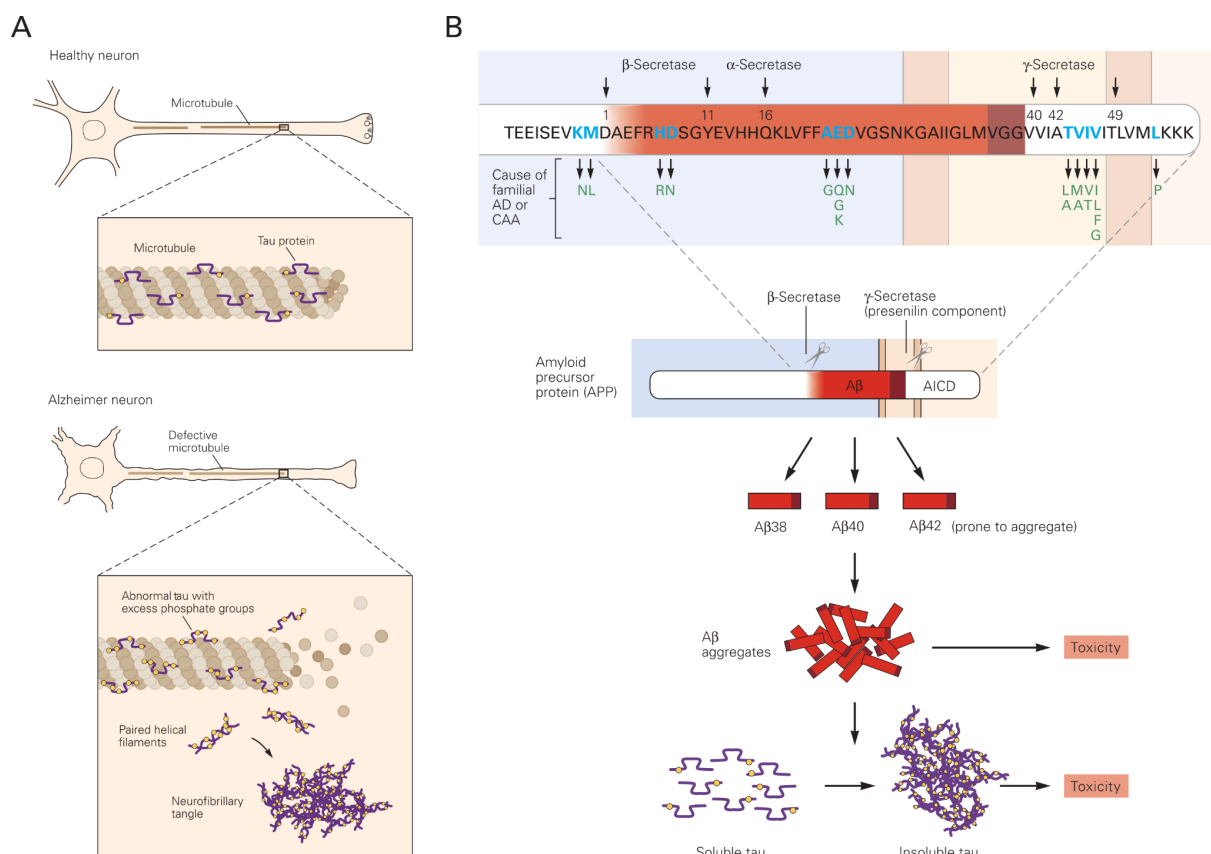


Figure 17. Tau and Aβ as hallmarks of Alzheimer's Disease Pathology. (a) Top: In healthy neurons, tau protein binds to and stabilizes microtubules; it is not found as paired helical filaments (PHFs). Bottom: In diseased neurons, tau becomes hyperphosphorylated, causing it to detach from microtubules, leading to their disassembly. The detached tau then aggregates into paired helical filaments (PHFs), which accumulate as neurofibrillary tangles. (b) The Aβ peptide is generated from APP by β-secretase and γ-secretase (Presenilin is the active catalytic unit of γ-secretase). Familial AD/CAA mutations (shown in green) in APP alter this

processing. A β generation, which predominantly occurs in endosomes, is modulated by synaptic activity and extracellular factors like ApoE and clusterin. The resulting A β aggregation (especially A β 42) is neurotoxic and promotes the conversion of soluble tau into aggregated forms. Tau conversion is independently regulated by its own level, sequence, and phosphorylation status. Adapted from Kandel, 2018 (63).

Alzheimer's disease is associated with cytoskeletal abnormalities in neurons, which are essential for maintaining cell structure and transporting proteins and organelles within the cell. When the cytoskeleton is disrupted, axonal transport is impaired, compromising synaptic inputs and eventually leading to the death of neurons. One of the most common cytoskeletal alterations in Alzheimer's disease is the formation of neurofibrillary tangles. These tangles are filamentous inclusions found in the cell bodies and dendrites of neurons and consist of paired helical filaments made of hyperphosphorylated tau, a microtubule-binding protein. Normally, tau is soluble, but in Alzheimer's disease, it becomes insoluble, leading to tangle formation (Fig.17a). As the affected neurons die, these tangles remain as remnants, and the loss of neurons disrupts synaptic connections in brain regions critical for memory and cognitive functions. Another hallmark of Alzheimer's disease is the accumulation of amyloid deposits, or senile plaques. These plaques are extracellular deposits of amyloid beta (A β) surrounded by damaged axons, astrocytes, and microglia, which are inflammatory cells. Amyloid beta is derived from a larger protein called amyloid precursor protein (APP), which is found in the dendrites, cell bodies, and axons of neurons. While the normal function of APP is still unclear, it is known that APP is processed inside the cell to produce different forms of amyloid beta, including A β 40, A β 42, and A β 43. A β 42 and A β 43 tend to form amyloid fibrils more quickly than A β 40, and in Alzheimer's disease, mechanisms not yet fully understood lead to the production of more toxic forms of amyloid beta (Figure 17b). These longer forms promote the formation of fibrils and contribute to the progression of the disease.

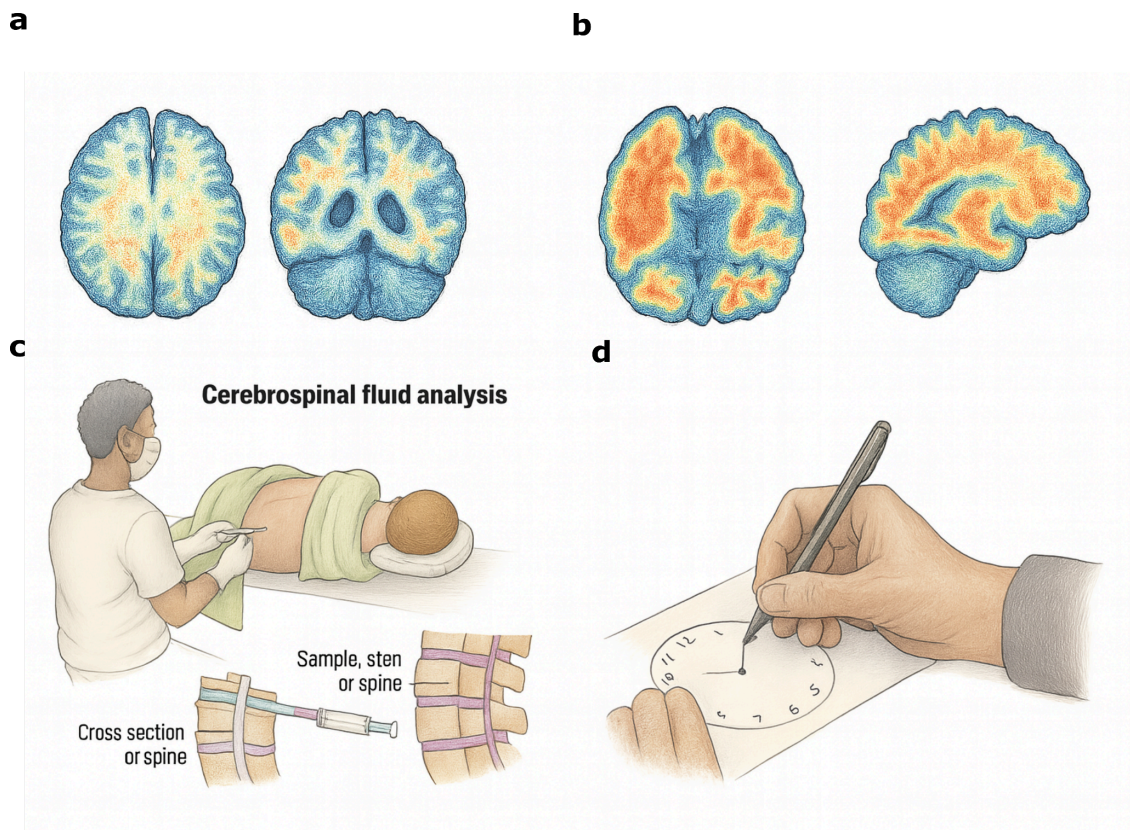


Figure 18. **Diagnostic hallmarks.** (a) Amyloid-PET; (b) Tau-PET, (c) Cerebrospinal fluid (CSF) collection, (d) Mini Mental Examination State (MMSE).

To diagnose Alzheimer's disease, doctors look for changes in the amount of amyloid peptides and Tau, in the cerebrospinal fluid or blood (Figure 18c). They also use imaging techniques, such as CT (Computerized Tomography), MRI, or PET (positron emission tomography) scans, to check for brain abnormalities, like shrinkage in the medial temporal lobe or reduced blood flow in certain areas (Fig.18 a and b). These findings are combined with cognitive and neurological assessments, such as the Mini Mental State Examination (MMSE), a widely used tool to evaluate cognitive function and monitor decline (Fig.18d). The MMSE includes tasks like drawing a clock, recalling words, identifying one's own location, and so on.

Considering its complex, multifactorial nature, understanding AD development and progression requires an integrated perspective that bridges alterations in brain structure, neural dynamics, and cognitive decline. AD is increasingly considered a disconnection syndrome (121,122), resulting from impaired communication within large-scale networks. In response, research has moved toward holistic approaches that investigate inter-regional brain interactions across different spatial and temporal scales (123,124).

However, no consistent pattern of alterations has emerged across studies (122). One possible reason may be that traditional network approaches disregard the dynamics of the interactions. Functional Connectivity (FC), for instance, represents the average statistical dependencies between brain regions over a given time interval, assuming relatively stable networks during rest (123,125,126). Yet, complex cognitive processes require the dynamic recruitment of different brain areas to respond to changing environmental demands (127), a capacity that may be compromised in AD (128–130). To address this limitation, recent studies have focused on Functional Connectivity Dynamics (FCD). Rather than focusing on a single "snapshot" of connectivity, FCD analyzes fluctuations in connectivity patterns over time intervals, unveiling the dynamic nature of interactions between brain regions and capturing the brain's inherent flexibility and adaptability (131,132). These dynamics span from a strictly "order-driven" to a purely "random-driven" scenario, with optimal function likely occurring between these extremes (133).

Within this framework, a new metric called *fluidity* has been introduced to quantify the richness and adaptability of large-scale brain dynamics. Altered fluidity, either excessive or diminished, has been observed in various neurological diseases (55,133,134), where reduced fluidity may reflect rigid and stereotyped connectivity patterns, while excessive fluidity may reflect disorganized, uncoordinated activity.

At the onset of symptoms, AD patients typically show a slowing of brain rhythms (135,136), reflected in decreased power in higher-frequency bands (beta/gamma), and increased power in lower-frequency ones (theta/delta) (135,136). This high-to-low-frequency ratio is more pronounced in AD than in healthy individuals (135,136), suggesting that changes in fluidity are not uniform but instead vary across frequency bands, potentially correlating with distinct cognitive deficits. Based on this, we hypothesize that fluidity alterations in AD are frequency-dependent, potentially exhibiting opposite trends between higher and lower frequencies. Furthermore, these changes may reflect the impact of neuronal loss on cognitive function (Figure 19).

To test this hypothesis, we analyzed source-reconstructed EEG data from a cohort of 28 AD patients and 29 age-matched healthy controls, considering that, among cost-effective and non-invasive diagnostic measures, electroencephalography (EEG) could hint at synaptic dysfunction and individual altered neurophysiological traits (118). All patients underwent lumbar puncture to quantify CSF biomarkers (A β 42, p-tau, and t-tau), and cognitive

performance was assessed using the Mini-Mental State Examination (MMSE). For each canonical frequency band, we characterized brain dynamics from the EEG data in terms of fluidity. The results reveal frequency-specific disruptions in AD: an elevation and reduction of fluidity of theta and beta band dynamics, respectively. Reduced beta fluidity correlates with higher cerebrospinal tau levels, suggesting a link with tau-related neurodegeneration. Furthermore, incorporating beta band fluidity into a regression model significantly improved the prediction of cognitive performance, underscoring its added value as a functional marker of clinical impairment. By capturing temporal variability in network interactions, fluidity offers a novel functional perspective on AD-related disconnection. This non-invasive, cost-effective metric may enhance early diagnosis and monitoring of disease progression, highlighting the potential of EEG-based dynamic biomarkers in neurodegenerative research.

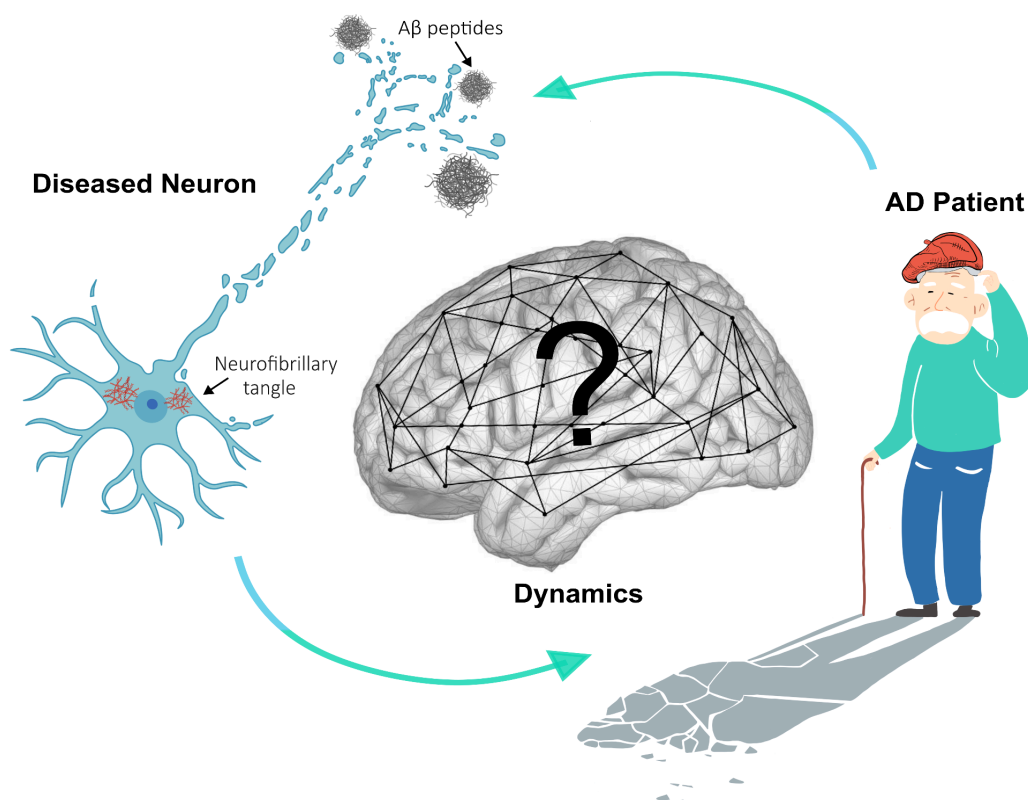


Figure 19. Conceptual framework of the study. The figure illustrates the progression of Alzheimer's disease (AD) from the cellular to the systemic level. The left panel shows the core pathology: progressive neuronal death and its associated biomarkers, amyloid-beta and tau proteins. This pathology leads to severe cognitive decline, symbolically represented on the right by a confused patient whose dissolving shadow highlights the loss of identity and function. Although these cellular and clinical manifestations are well-established, we lack understanding of AD's impact on large-scale brain dynamics. The central panel depicts the brain as a dynamic network whose flexible functional configurations may be compromised. Our study investigates whether this neuronal death causes measurable alterations in brain network dynamics, which could provide crucial new insights into AD pathophysiology.

3.1 Data acquisition

Sex	Age	MMSE	Ab42	tTau	pTau
F	76	14	627	618	82.5
M	77	24	495	493	63.1
F	77	23	600	1093	164.6
M	69	24	455	641	98.1
F	80	21	536	481	60.7
F	70	13	510	508	75.7
M	60	8	404	907	163.4
F	68	21	582	665	93.7
F	67	22	663	1461	206.0
M	64	6	476	687	102.2
M	70	23	420	416	81.2
M	81	24	756	1235	203.2
F	72	27	341	418	54.6
F	70	30	822	551	76.4
M	74	30	263	311	35.9
M	71	15	359	491	61.5
F	76	18	487	925	141.8
F	65	17	544	860	129.8
F	77	25	572	539	77.2
F	80	14	403	641	67.6
M	68	25	676	618	88.1
F	80	27	576	477	64.4
M	64	22	461	2000	325.9
F	73	21	719	654	86.6
F	71	20	677	611	88.0
F	80	27	867	645	96.7
M	79	23	438	739	106.9
M	64	15	464	346	49.3

Table 1. Demographic and Clinical Characteristics of Study Participants. A general summary of the key characteristics for all participants, encompassing sex, age, cognitive status as measured by the Mini-Mental State Examination (MMSE) score, and cerebrospinal fluid (CSF) biomarker levels of A β 42, total tau (t-tau), and phosphorylated tau (p-tau).

The participants in this study were recruited at the Neurology Unit of the Department of Biomedicine, Neuroscience and Advanced Diagnostics (Bi.N.D.) of the University of Palermo, Italy. They included both patients with Alzheimer’s Disease and healthy volunteers. All participants went through a careful clinical and cognitive evaluation.

The evaluation started with a detailed medical and neurological history, collected in the presence of a caregiver or a close relative to make the information as accurate as possible. We

collected demographic data (such as age, sex, and education level), medical history (including psychiatric symptoms, vascular and metabolic risk factors, medications, and other illnesses), and family history of dementia or neurological disorders. Then, experienced neurologists performed a neurological examination to check for any signs of other diseases that could affect the brain or nervous system.

Cognitive functioning was assessed with the Mini-Mental State Examination (MMSE), a short and widely used test that evaluates several cognitive abilities such as orientation, memory, attention, calculation, language, and visuospatial skills. The test gives a score from 0 to 30: higher scores indicate normal cognitive abilities, while lower scores reflect different levels of impairment. All the demographic and clinical measures of AD patients are shown in Table 1.

After the clinical and cognitive assessment, participants underwent a resting-state EEG recording. EEG was chosen because it has excellent temporal resolution and can detect changes in brain network activity that may appear before structural damage is visible.

EEG recordings were performed for ten minutes. During the procedure, participants were asked to remain awake and relaxed, with their eyes closed for the first five minutes and open for the following five minutes. Cortical activity was recorded using 21 scalp electrodes positioned according to the international 10–20 system (Fp1, F3, C3, P3, O1, F7, T3, T5, Fpz, Fz, Cz, Pz, Oz, Fp2, F4, C4, P4, O2, F8, T4, T6), with the reference placed between Cz and Oz. The EEG signals were acquired with a sampling frequency of 256 Hz and filtered using a band-pass filter between 1.5 and 40 Hz. Eye movements, both horizontal and vertical, were also monitored, with a frequency band between 0.3 and 70 Hz. Electrode impedance was kept below 5 k Ω to ensure signal quality. None of the participants were taking acetylcholinesterase inhibitors or NMDA receptor antagonists at the time of EEG acquisition.

To obtain biological markers of the disease, we also performed a lumbar puncture to collect cerebrospinal fluid (CSF) samples. This was done following international safety standards, and participants were carefully monitored to minimize any discomfort. The CSF was analyzed for typical Alzheimer's biomarkers, including A β 42 (or A β 42/40 ratio), total tau (t-tau), and phosphorylated tau (p-tau). A CSF profile consistent with Alzheimer's disease was defined by low A β 42 or A β 42/40 levels together with high p-tau levels, indicating the presence of amyloid and tau pathology.

When available, we also used FDG-PET scans to study brain metabolism. A pattern consistent with Alzheimer's disease is characterized by reduced glucose metabolism in specific brain areas, such as the hippocampus, temporal and parietal regions, posterior cingulate cortex, and precuneus. This kind of scan can provide additional information to support the clinical and biological diagnosis.

Inclusion criteria for patients were designed to select people in the early stages of the disease. Patients needed to have a diagnosis of Alzheimer's disease dementia according to established criteria (NINCDS-ADRDA and AT(N)) or a diagnosis of mild cognitive impairment (MCI) due to Alzheimer's disease according to the 2011 NIA-AA criteria, and an MMSE score above 17.5. This allowed us to focus on individuals with mild or moderate symptoms, where brain changes can be detected more clearly.

Healthy controls had to be older than 50 years, show normal cognitive performance (MMSE score above 28), maintain full independence in daily life, and not report any subjective cognitive problems. This helped ensure a good comparison between patients and healthy individuals.

Exclusion criteria were applied to everyone in order to remove possible confounding factors. People with psychiatric disorders (such as depression or psychosis), other neurological diseases (such as stroke, Parkinson's disease, or epilepsy), those taking psychotropic medications, cholinesterase inhibitors, or NMDA antagonists, as well as people with untreated thyroid or adrenal disorders or advanced liver disease, were not included. This made the sample as clean and specific to Alzheimer's disease as possible.

3.2 EEG Preprocessing

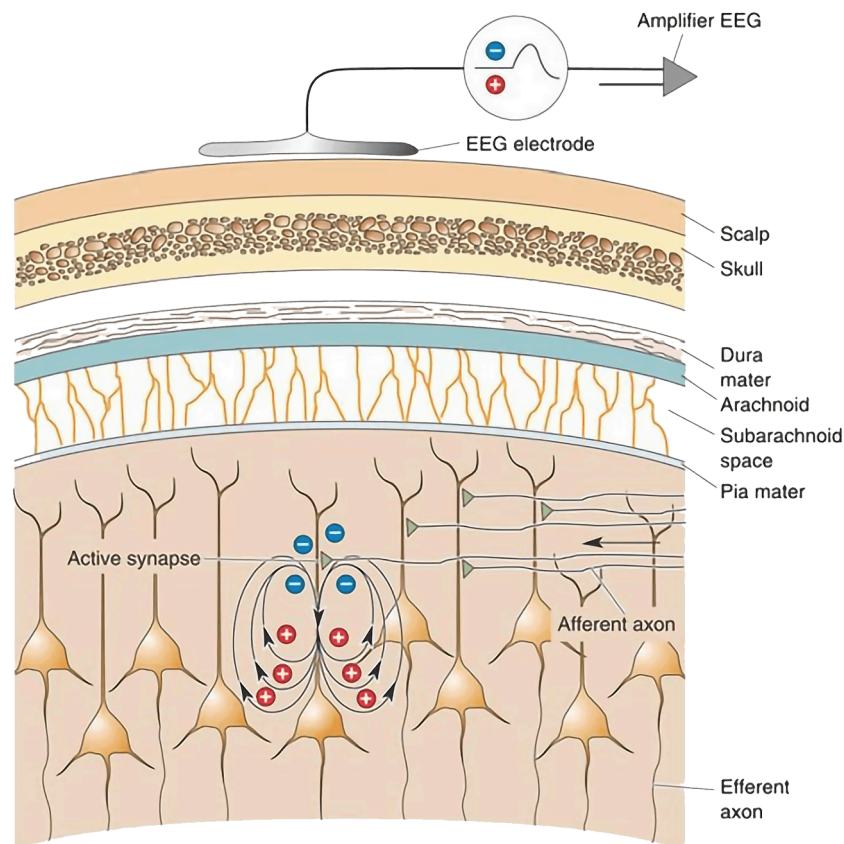


Figure 20. Generation of extracellular electrical fields by summed synaptic currents in pyramidal neurons. An excitatory postsynaptic potential (EPSP) initiated on an apical dendrite by glutamate release results in inward cation flux, creating a negative current sink in the extracellular space near the synapse and a corresponding positive current source in deeper, more basal dendritic regions where the current exits the cell. The EEG electrode measures the superposition of these small, spatially separated extracellular potentials, which must be generated synchronously across thousands of cells to yield a scalp-detectable signal (Note: EEG convention plots negativity upward). Adapted from *Neuroscience: exploring the brain*, 3rd edition.

The electroencephalogram (EEG) measures extracellular postsynaptic currents generated primarily by pyramidal neurons, which are oriented perpendicularly to the cortical surface (Figure 20). This specific orientation allows the electric fields produced by groups of neurons to summate when they fire synchronously, resulting in signals that can be detected at the scalp level. However, during EEG recordings, neural activity is often contaminated by different types of noise, including physiological sources (such as muscle activity, eye movements, cardiac activity, respiration, and sweating), environmental interference (for example, from power lines or electromagnetic fields), equipment-related issues (such as impedance mismatch, cable movement, or amplifier noise), and external disturbances from nearby electronic devices or vibrations.

To obtain cleaner and more reliable data, EEG signals must undergo careful preprocessing. In this study, 19 standard scalp electrodes were analyzed, excluding the reference channels. Data was processed using EEGLAB (v.14.2.2b.22). The raw EEG signals were first downsampled to 256 Hz and then band-pass filtered between 2 and 45 Hz using a finite impulse response (FIR) filter with a Hamming window. This filtering step helps remove unwanted frequency components, such as low-frequency drifts and high-frequency noise, improving the signal-to-noise ratio. Preprocessing focused exclusively on the eyes-closed condition, which is less affected by visual input and is known to produce more stable and stronger alpha-band activity, making it particularly suitable for resting-state analyses.

Bad channels were automatically identified based on their statistical deviation from the mean signal and subsequently removed. Signal cleaning was performed using the `pop_clean_rawdata` function in EEGLAB, which automatically detects and eliminates flat channels, noisy segments, and power-line noise. This standardized and automated pipeline was designed to enhance reproducibility, reduce human bias, and save time, while allowing flexible criteria for artifact detection. Noisy channels were then interpolated using the spherical spline interpolation method to preserve the spatial consistency of the EEG data.

To further separate neural signals from artifacts, Independent Component Analysis (ICA) was applied. ICA is a mathematical method used to separate a mixed signal into its different sources. In EEG, the signal recorded at each electrode is actually a combination of brain activity and different types of noise. ICA decomposes the EEG signal into independent components representing different sources, such as brain activity, eye blinks, muscle movements, or cardiac signals. In this case, ICA is used to identify and remove signal components associated with artifacts or muscle activity. Components were classified using the `ICLabel` plugin, which provides automatic labeling of sources, and non-brain components were excluded from further analysis. Each component's topography and time series were visually inspected to verify correct classification and ensure precise artifact removal. Figure 21 illustrates an example of components classified as related to brain activity.

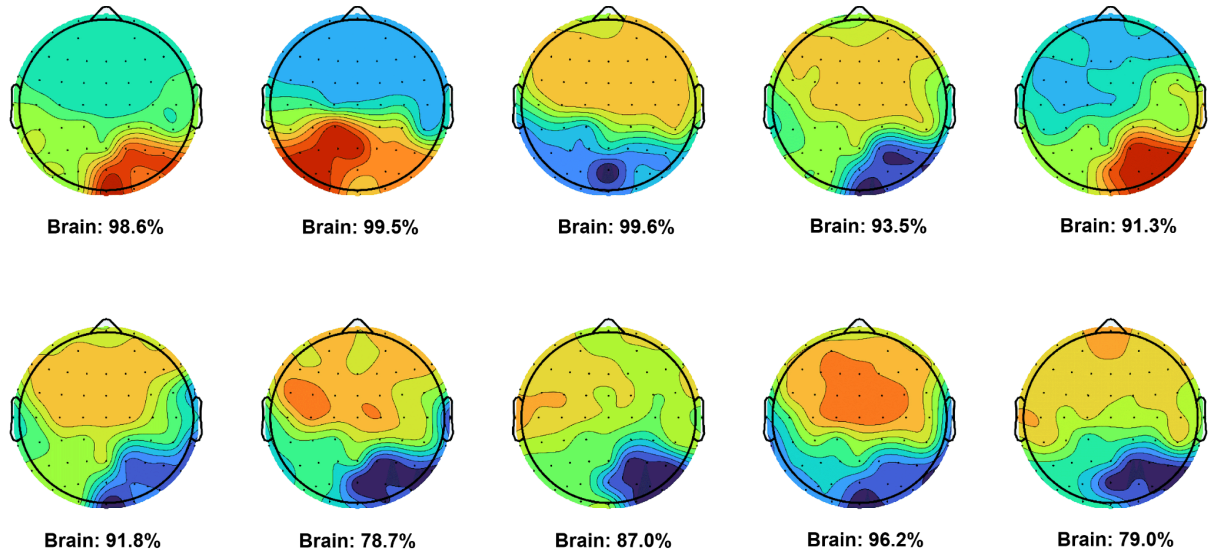


Figure 21. Spatial maps of brain Independent Component Analysis (ICA) components obtained from EEG data. The percentages indicate the estimated probability that each component represents neural (brain) activity rather than artifacts.

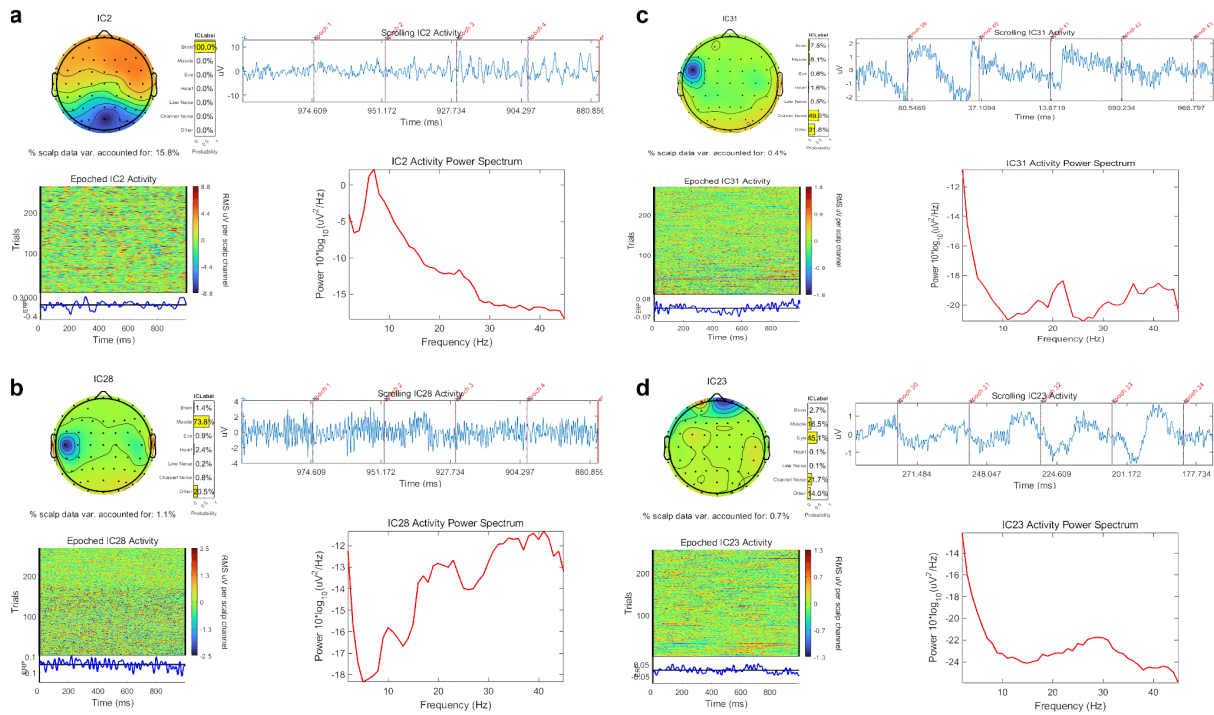
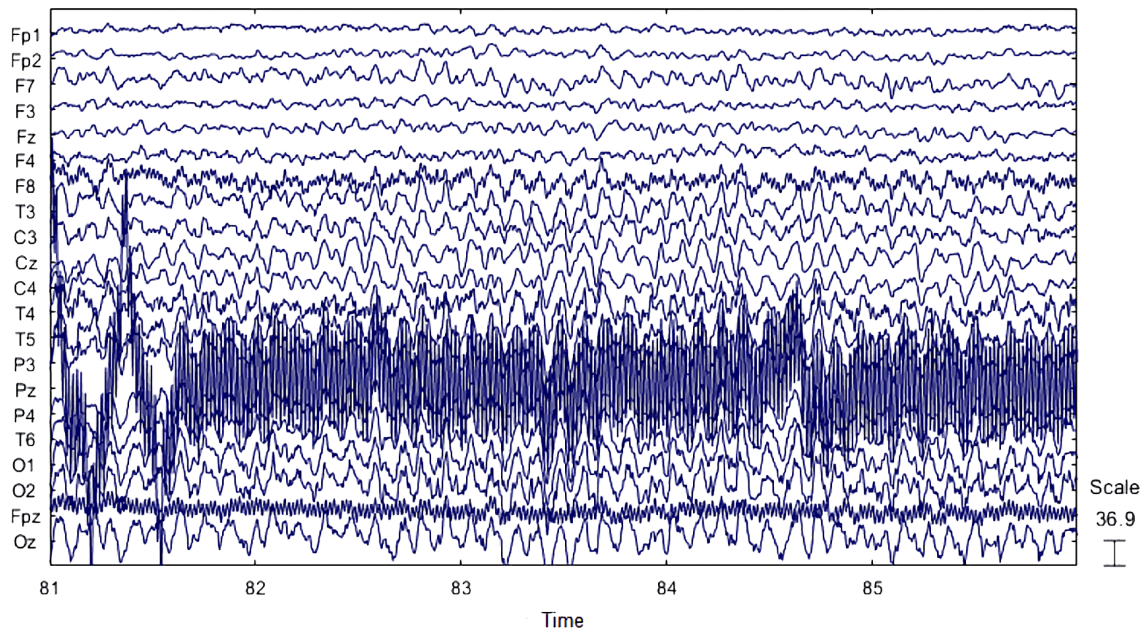


Figure 22. Neural and non-neural independent components. (a) Example of a neural activity component compared with components reflecting (b) muscle activity, (c) channel noise, and (d) eye activity. Muscle-related components exhibit strong power in the high-frequency range of the spectrum.

Panel (a) of Figure 22 shows a neural activity component, which is compared with examples of components related to muscle activity (b), channel noise (c), and eye activity (d). For muscle components, the spectrum shows a strong power in the high-frequency range. The

ERP-image is very noisy, and these components are often only transiently active during experiments, typically affecting a subset of trials, after which the data return to normal. For eye components, the spectrum usually exhibits a characteristic peak around 30 Hz. In contrast, for channel noise, the time course often shows abrupt jumps and irregular fluctuations.

a



b

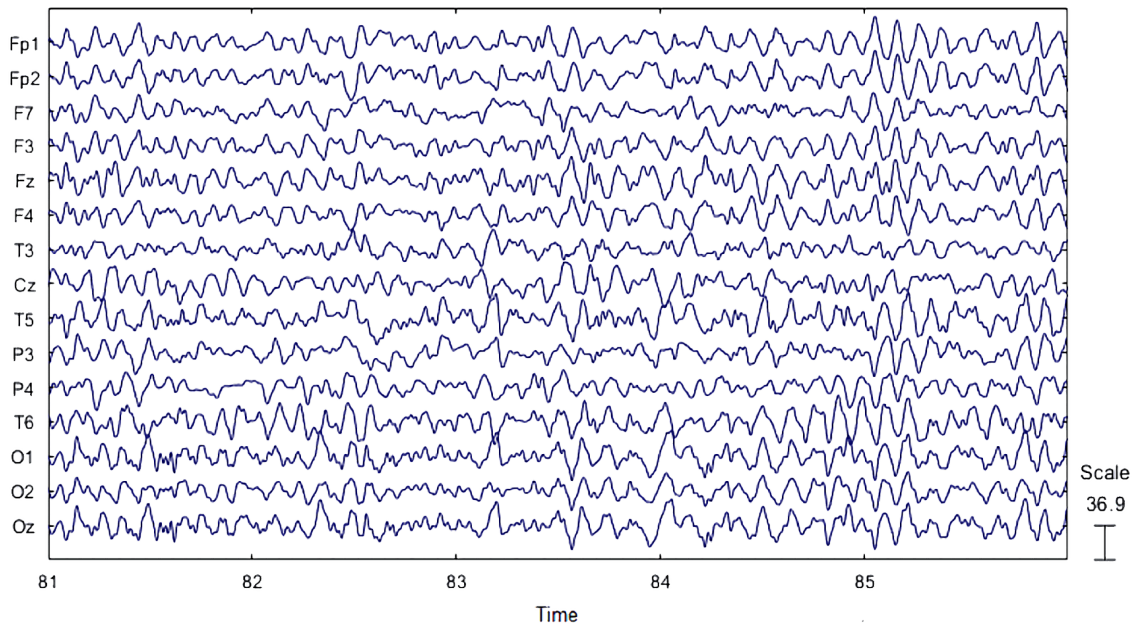


Figure 23. Time course of EEG signals before (a), and after (b) running the cleaning pipeline.

This multistep cleaning procedure was essential to isolate true neural activity from various noise sources and improve the quality of the EEG signal (Figure 23.) where the EEG signal is shown before and after signal cleaning.

3.3 Source Reconstruction

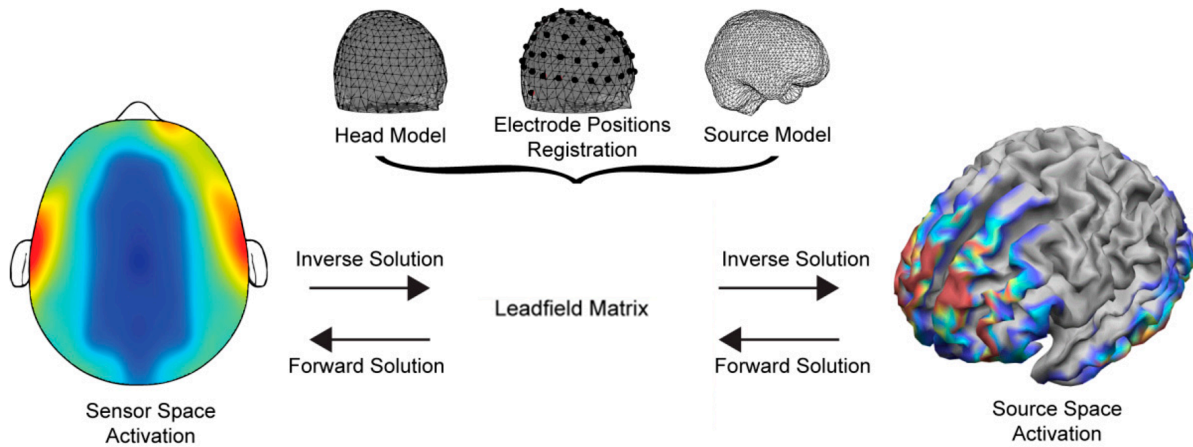


Figure 24. Schema of EEG Source Localization. This diagram illustrates the process of localizing the activity of brain sources from scalp electroencephalography (EEG; sensor-space) recordings. The relationship is governed by the Leadfield Matrix, which maps activity from the estimated Source Model (neuronal sources within the brain) to the observed data in the Sensor Maps (scalp electrodes). The Leadfield Matrix is derived from the Head Model (geometric and conductivity properties of the head) and the Electrode Position Registration (precise electrode locations). The inverse problem aims to use the Sensor Maps and the Leadfield Matrix to estimate the Source Model.

After preprocessing, source reconstruction was performed. Source reconstruction aims to estimate the brain regions that generate the EEG signals recorded at the scalp. This process involves building a mathematical model that links the underlying neural activity (sources) to the signals measured by the electrodes. Two models are used: the forward model, which predicts how electrical activity spreads from known sources in the brain to the electrodes, and the inverse model, which works in the opposite direction, estimating the sources of the recorded EEG signals based on the forward model (Figure 24).

Several key components are essential for accurate source reconstruction: the leadfield matrix, the head model, the electrode position registration, and the source model. The leadfield matrix describes how each brain source contributes to the signals at each electrode and is derived from the forward model. It has dimensions $M \times N$, where M is the number of electrodes and N the number of neural sources. Each element of the matrix represents the

sensitivity of a specific sensor to a specific neural source. The head model represents the geometry and conductivity of the scalp, skull, and brain, accounting for the way electrical signals travel through these tissues. Electrode position registration ensures that electrode positions on the scalp are accurately aligned with the head model. Finally, the source model defines the location of possible brain sources, typically represented as a grid or a set of dipoles constrained to the cortical surface. Combining these elements allows the estimation of the brain regions underlying the scalp EEG activity, linking measured signals to their neural generators.

In this study, source reconstruction was performed using Brainstorm, an open-source toolbox for EEG and MEG analysis. Forward modeling can be achieved through various methods, such as the Boundary Element Model (BEM) or the Finite Element Method (FEM). These methods use anatomical information from structural MRI scans to model the geometry and conductivity of different tissue compartments (e.g. scalp, skull, brain) and simulate how electrical currents propagate through these tissues to the scalp electrodes. The difference between BEM and FEM lies primarily in the mathematical and computational techniques used to model and solve problems in various engineering and scientific fields: BEM is a numerical technique used for solving partial differential equations by discretizing only the boundaries of the domain of interest, while the FEM solves partial differential equations by discretizing the entire domain of interest, making it more computationally intensive. In Brainstorm, we can choose between the 3-shell spherical model, the OpenMEEG BEM, and the DUNEURO FEM, which differ in how they represent head conductivity and geometry, as well as in their computational complexity and accuracy. In particular:

- 3-shell spherical model: the shape of the brain is assumed to be spherical, which is very fast but less precise.
- OpenMEG BEM has boundary elements that follow the precise shape of the head. Each compartment (scalp, skull, and brain) is assigned a specific isotropic conductivity, meaning that the conductivity is constant throughout the compartment and identical in all directions;
- DUNEURO FEM uses a tetrahedral mesh, which represents the volume of the head. It can include 5 layers.

We chose the OpenMEEG BEM because it provides a good balance between accuracy and computational efficiency, which is particularly appropriate given the limited number of electrodes used in our recordings.

First, individual MRIs were segmented using the CAT12 toolbox, and the cortical surface was downsampled to 15,002 vertices. The inner skull, outer skull, and scalp meshes were then discretized to 1,922 vertices. A realistic head model was created using the OpenMEEG BEM. The inverse solution was estimated using the weighted Minimum Norm Estimation (wMNE) method, with dipole orientations constrained to be normal to the cortical surface, and Brainstorm's default parameter settings were applied. Finally, reconstructed source activity was downsampled to the Desikan–Killiany anatomical atlas by averaging the time series of the vertices belonging to each region of interest.

3.4 Fluidity

Resting-state brain activity is highly organized, showing structured patterns of activation across different brain regions. Functional Connectivity (FC) measures capture the coordination between brain regions, providing a static view of these connections (137). However, these patterns continuously change, and dynamic Functional Connectivity (dFC) measures track how FC evolves over time by analyzing different time windows (131). This dynamic nature reflects the brain's ability to transition between multiple activity patterns, forming a functional repertoire. Fluidity represents this flexibility, as the brain explores a wide range of states, supporting complex and adaptive dynamics (132). To measure functional connectivity, we can use the Phase Locking Value (PLV) instead of standard correlation methods like Pearson's (138). The PLV measures how consistent the phase difference between two brain regions remains over time. The idea is that if two brain regions are functionally connected, the difference between their phases should remain consistent over time. The PLV measures how consistent the phase relationship between two signals is over time. It is computed across multiple trials or epochs as follows:

$$PLV(t) = \frac{1}{N} \left| \sum_{n=1}^N e^{i\theta(t,n)} \right|$$

Here, $\theta(t,n)$ is the phase difference between two signals at time t and trial n , and N is the number of trials.

Since the instantaneous phase has a physical interpretation only for narrowband signals, the first step in computing the Phase Locking Value (PLV) is filtering the data within the desired frequency band. The PLV was calculated in the canonical frequency bands: theta (4-8 Hz), alpha (8-14 Hz), beta (14-30 Hz), and gamma (30-40 Hz). Next, the instantaneous phase is extracted using the Hilbert transform, which converts real signals into a complex representation.

The PLV quantifies phase synchrony between two signals and ranges from 0 to 1:

- PLV = 0: No phase synchrony (random phase differences).
- PLV = 1: Perfect phase synchrony (identical phase differences across trials).

To calculate PLV over time, rather than across trials, the original formula introduced by Lachaux et al. (1999) was adapted (138). It now considers a sliding time window to compute PLV as in Sadaghiani et al., 2019 (139):

$$PLV = \frac{1}{N} \left| \sum_{n=1}^N e^{i(\phi_{reg1}(n) - \phi_{reg2}(n))} \right|$$

where N is the number of time points within the window, whose length varied depending on the frequency band analyzed. We used Hilbert transform to calculate the analytic phase at the time point n for the region x: $\phi_{reg1}(n) = \arctan\left(\frac{u(n)}{v(n)}\right)$, where v is the real part of the analytic signal and u is the Hilbert transform of the imaginary part of the signal. So, $\phi_{reg1}(n) - \phi_{reg2}(n)$ represents the phase difference between the two signals (recorded in regions 1 and 2) at the time point n. The PLV was computed for each sliding window and then averaged across all region pairs.

Using this approach, we can construct a dynamic Functional Connectivity (dFC) matrix, which reflects the time-varying connectivity between different brain regions as in Breyton et al. (134):

$$FC_{ij}(t) = FC[s_i(t'), s_j(t')] \text{ with } t' \in \left[t - \frac{\tau_{win}}{2}; t + \frac{\tau_{win}}{2} \right],$$

$$FC(t) \in R^{N \times N}, \text{ for } N \text{ sources (or electrodes) in the network}$$

where FC(t) reflects the time-varying connectivity between different brain regions.

Subsequently, Functional connectivity dynamics (FCD) was then calculated by correlating the upper triangular part of PLV matrices from consecutive windows, capturing the temporal evolution of inter-regional synchronization.

$$dFC(t_1, t_2) = \text{corr}[UpperTri(FC(t_1)), UpperTri(FC(t_2))]$$

$$dFC(t_1, t_2) \in R^{M \times M}, \text{ for } M \text{ windows}$$

The fluidity was then defined as the variance of the upper triangle of the FCD matrix, after removal of the overlapping windows:

$$fluidity = \text{Var}[UpperTri(dFC - B)]$$

$$B_{ij} = 1 \text{ if } \left[t_i - \frac{\tau_{win}}{2}; t_i + \frac{\tau_{win}}{2} \right] \cap \left[t_j - \frac{\tau_{win}}{2}; t_j + \frac{\tau_{win}}{2} \right] \neq \emptyset; 0 \text{ otherwise}$$

with the diagonal offset to compute *fluidity* given by the following formula:

$$offset = \frac{n_{overlap}}{t_{win} - n_{overlap}} + 1$$

This approach generated a time-resolved functional connectivity matrix that captures how synchronization between brain regions evolves over time. The temporal variability of functional connectivity served as a proxy for the brain's dynamic adaptability, where higher variance corresponds to a stronger tendency to spontaneous network reorganization. A graphical representation of how the fluidity is computed is shown in Figure 25.

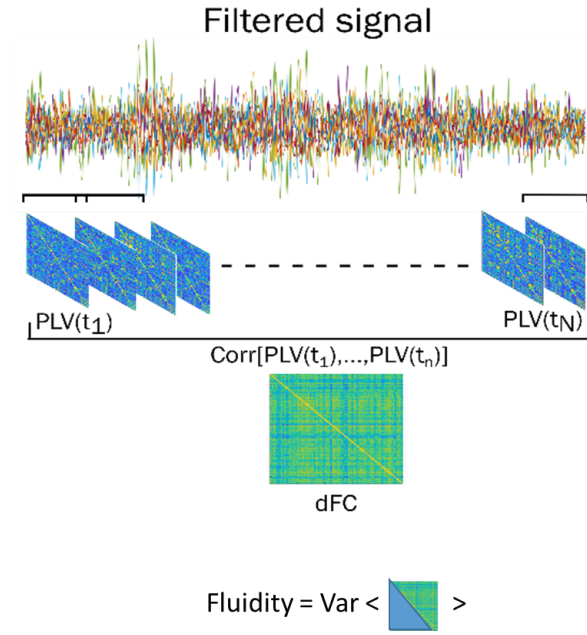


Figure 25. After band-pass filtering the signal, time-windowed analysis was performed to generate average FC per time-window, via the PLV. The correlation of the vectorized PLV matrices yields the dFC matrix. The variance of its upper triangular is a metric of brain fluidity.

3.5 Statistical Analysis

For each participant, the mean fluidity across all connectivity matrices was computed separately for the Alzheimer's disease (AD) and control groups. To determine whether the difference between the two groups was statistically significant, a non-parametric permutation test was employed.

This procedure involved repeatedly shuffling the group labels while preserving the original group sizes, thereby generating a null distribution of mean differences under the assumption of no relationship between group membership and fluidity. In each of the 20,000 permutations, the absolute difference between group means was calculated, resulting in an empirical estimate of the null distribution. The observed difference between groups was then compared to this distribution, and the p -value was derived as the proportion of permuted differences exceeding the observed value. This distribution-free approach provides a robust alternative to classical parametric testing, as it does not rely on the assumption of normality.

In addition, Pearson's correlation was used to assess associations between fluidity and other variables of interest, with a significance threshold set at $p < 0.05$.

3.6 Multilinear Model

A multilinear model, also known as a multiple linear regression model, is a statistical tool used to examine the relationship between one dependent variable (or outcome) and several independent variables (or predictors) at the same time.

The main idea is to understand how changes in the predictors are associated with changes in the outcome, while controlling for the influence of the other variables in the model.

In its simplest form, the model assumes that the outcome can be expressed as a linear combination of the predictors plus an error term. Mathematically:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \dots + \beta_n X_n + \varepsilon$$

Where:

- Y is the dependent variable;
- $X_1, X_2, \dots, X_n$ are the predictors;
- β_0 is the intercept;
- $\beta_1, \beta_2, \dots, \beta_n$ are the regression coefficients, which indicate the contribution of each predictor to the outcome;
- ε in the error term.

One of the strengths of multilinear models is that they allow the evaluation of each variable's independent effect while holding the others constant, helping to identify which variables contribute most towards explaining variability in the outcome.

For this reason, to further examine the potential of fluidity as a biomarker of Alzheimer's disease and its association with clinical outcomes, a multiple linear regression model was constructed to predict cognitive performance, calculated by the Mini-Mental State Examination (MMSE) score. The use of this model allowed the evaluation of the independent

contribution of fluidity while accounting for the influence of established demographic and biological factors.

In addition to fluidity, three covariates were included in the model: age, sex, and total tau (tTau) levels. All predictor variables were standardized using z-scores prior to model fitting, ensuring that they were placed on a comparable scale. This facilitated the interpretation of regression coefficients and allowed meaningful comparisons of their relative contributions to MMSE.

To evaluate the model's predictive performance and generalizability, a leave-one-out cross-validation (LOOCV) procedure was implemented. The LOOCV is a statistical technique used to evaluate how well a model can generalize to new, unseen data. In other words, it tests the model's predictive performance and helps reduce the risk of overfitting, which occurs when a model fits the training data very well but performs poorly on new data. The key idea is simple: the dataset is divided into training and testing sets, but instead of holding out a large portion of the data, only one observation is left out at a time. The model is trained on all the remaining data and then tested on the single left-out observation.

In this case, at each iteration, one subject was excluded from the training set and used as the test case, while the model was fitted on the remaining participants.

Moreover, multicollinearity among variables was evaluated using the Variance Inflation Factor (VIF), ensuring that observed effects were not confounded by strong interdependencies between predictors.

Overall, this modeling framework made it possible to test whether fluidity was associated with cognitive impairment and to determine its relative weight compared to traditional demographic and pathological markers. By integrating functional and clinical information, this approach provides a more comprehensive understanding of fluidity as a potential functional biomarker capable of capturing dynamic features of brain network organization that may not be fully explained by conventional measures.

3.7 Analysis Pipeline

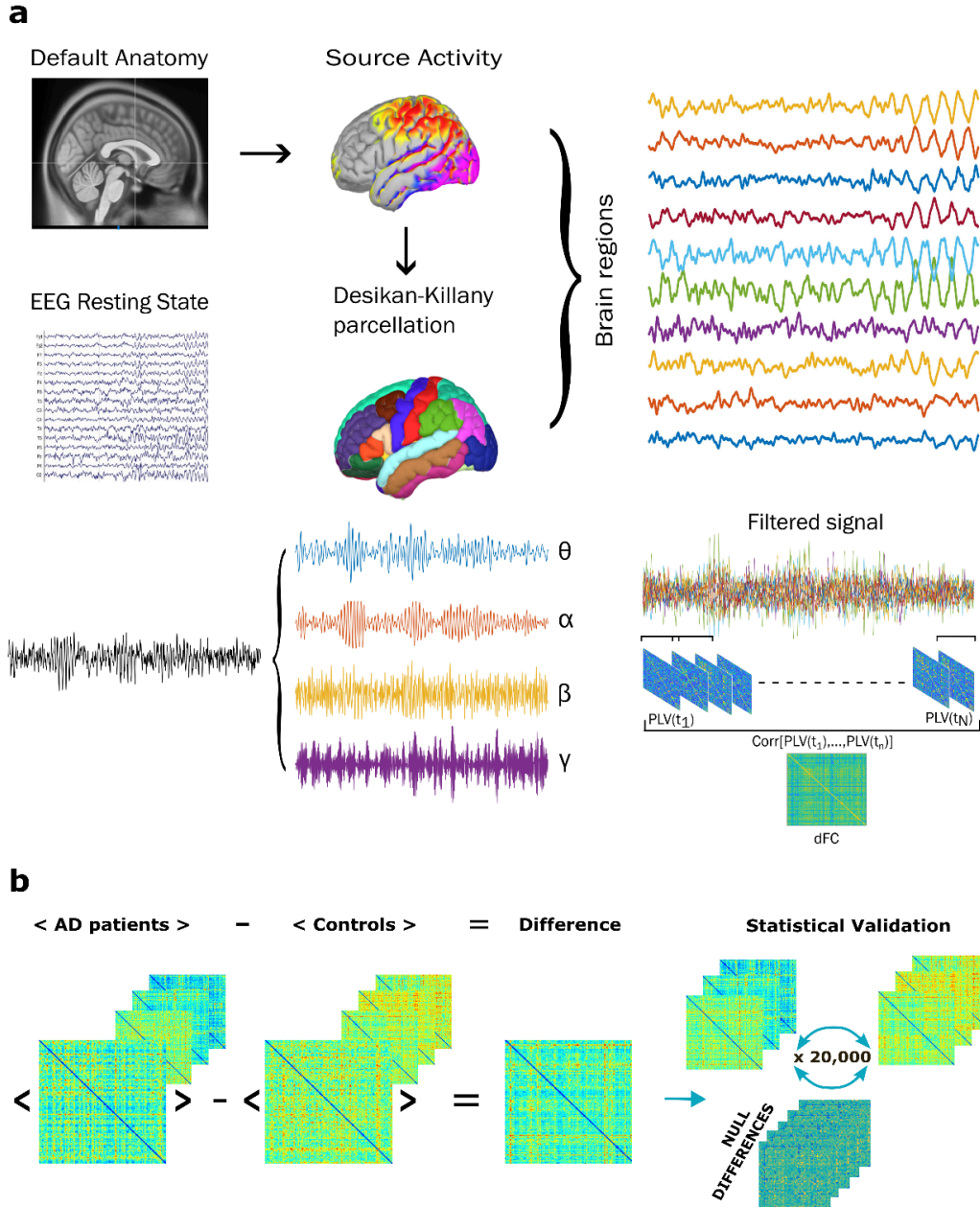


Figure 26. Overview of the analysis pipeline. (a) The analysis began with EEG signals acquired from both Alzheimer's disease (AD) patients and healthy controls. After standard preprocessing, source reconstruction was performed using a Default Anatomy to localize brain activity into 68 cortical regions defined by the Desikan-Killiany atlas. This activity was then filtered into canonical frequency bands. To capture dynamic interactions, functional connectivity dynamics were assessed using the Phase Locking Value (PLV). The PLV was computed over sliding windows, providing a time-resolved measure of phase synchronization across all brain regions. Finally, the variance of these dynamic connectivity patterns was quantified, which served as our primary measure of network fluidity. (b) Our primary objective was to assess whether the overall average fluidity differed significantly between the AD and control groups. For each subject, the mean fluidity value from the time-by-time matrix was first computed. We then compared the average of these mean values between the two groups. To rigorously validate any observed difference, a non-parametric permutation test was employed. This involved randomly shuffling the group labels (AD or control) across all subjects (20,000 times). In each iteration, the absolute difference in group means was recomputed, which generated a null distribution of differences under the hypothesis that no true difference exists in the network dynamics between the two cohorts.

In summary, our aim was to explore whether elements of brain dynamics correlate with the presence of pathological markers and clinical disability. By doing so, we attempt to determine whether fluidity could serve as a predictive marker for this neurodegenerative condition. This hypothesis is grounded in the premise that deviations in the temporal variability of connectivity may reflect underlying disease processes. As illustrated in Figure 26, the analysis began with the preprocessing of EEG data for both AD patients and healthy controls, which included filtering and artifact removal to ensure clean and reliable signals. Source reconstruction was then performed using a standard anatomical model to estimate cortical activity from the recorded scalp potentials. The brain was parcellated into 68 regions of interest according to the Desikan–Killiany atlas.

To investigate neural dynamics across different temporal scales, the reconstructed signals were decomposed into canonical frequency bands: theta (4–8 Hz), alpha (8–14 Hz), beta (14–30 Hz), and gamma (30–40 Hz). Functional connectivity between regions was then assessed using the Phase Locking Value (PLV), a widely used measure of phase synchronization. Higher PLV values indicate stronger phase coupling and more robust inter-regional communication, whereas lower values reflect weaker interactions. PLV was computed within sliding windows to capture time-varying connectivity. Pearson’s correlation was then applied between PLV matrices from consecutive windows, resulting in a dynamic functional connectivity (dFC) matrix that reflects the temporal evolution of inter-regional synchronization. Finally, the variance of PLV across windows was calculated to quantify network fluidity, representing the brain’s ability to dynamically reorganize its connectivity patterns over time. This measure provides functional insight into disease-related alterations in network dynamics.

3.8 Results

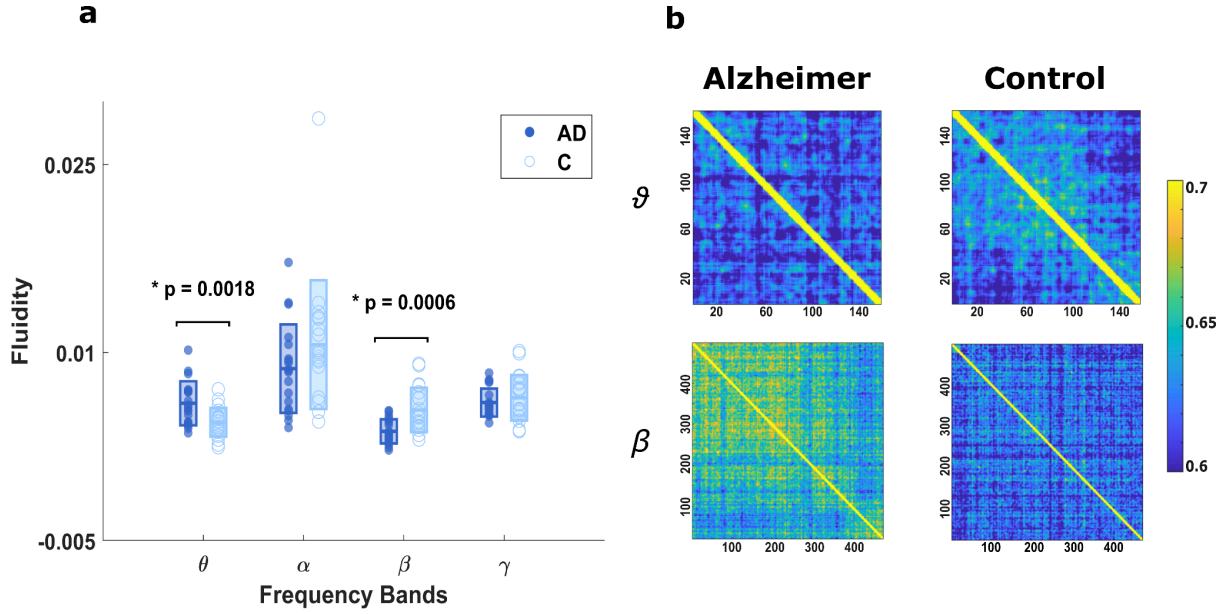


Figure 27. Significant group differences in fluidity between control and AD patients were observed only across theta and beta bands. (a) The distribution of individual fluidity values across four canonical frequency bands, theta (4–8 Hz), alpha (8–14 Hz), beta (14–30 Hz), and gamma (30–40 Hz), was obtained. Significant group differences were noted as the AD patients showed markedly higher fluidity in the theta band ($p = 0.0018$) but, conversely, lower fluidity in the beta band ($p = 0.0006$) compared to healthy controls. (b) The group-averaged fluidity matrices illustrate these findings for the theta (top) and beta (bottom) bands in both AD patients (left) and controls (right). In AD, the similarity across time is apparent in the beta band (stronger correlation), indicating lower variability and reduced network flexibility. Oppositely, the theta-band dynamics vary more across time in AD, suggesting a fundamental alteration in how network flexibility is distributed across the brain's operating frequencies.

It was assumed that communication between two brain regions occurs within the same frequency band and relies on synchronization mechanisms. Based on this assumption, it was hypothesized that patients with Alzheimer's disease (AD) might exhibit a reduced number of brain states, resulting in lower fluidity compared to healthy controls. To test this hypothesis, fluidity was analyzed for each canonical frequency band (theta, alpha, beta, and gamma) across all participants.

Significant group differences emerged in the theta and beta bands (Figure 27a). Specifically, in the theta band, fluidity was significantly higher in AD patients compared to controls ($p = 0.0018$), whereas in the beta band it was significantly lower in AD patients ($p = 0.0006$). Figure 27b illustrates the FCD matrices averaged across all participants for both groups: AD (left) and controls (right), in the theta band (top) and beta band (bottom). Higher correlations (in yellow) indicate greater similarity between PLV matrices across time, which reflects the presence of fewer distinct connectivity states. In these cases, the matrices appear more stable and less variable, suggesting that the brain tends to remain “locked” in a restricted set of

network configurations with limited flexibility to transition between states. This pattern reflects an increase in network rigidity. On the other hand, lower correlations (in blue) indicate reduced similarity between PLV matrices over time, which reflects the presence of a greater number of distinct connectivity states. In this case, the matrices appear less stable and more variable, suggesting that the brain is able to transition more flexibly between different network configurations. This pattern reflects increased network fluidity and a greater capacity for dynamic reorganization.

Therefore, the effect was frequency-dependent. The increased fluidity observed in the theta band may reflect a compensatory mechanism that allows the brain to maintain large-scale functional integration despite neurodegenerative damage. Slower rhythms, such as theta, are typically associated with long-range communication and global integration, so this result may indicate the brain's attempt to reorganize and adapt to structural and functional disruptions. Conversely, the reduced fluidity in higher frequency bands, such as beta, may reflect a loss of fine-tuned local processing and decreased network efficiency, particularly in regions that normally rely on faster oscillatory activity to support precise, task-related communication.

This interpretation aligns with known functional roles of different oscillatory frequencies. Theta waves are typically associated with creativity, emotional connection, intuitive processing, and relaxed states. When they become overly prominent, they have been linked to daydreaming and attentional lapses, while their suppression can lead to anxiety and reduced emotional awareness. Beta waves, on the other hand, are involved in conscious thought, logical reasoning, and focused attention. Under normal conditions, they support goal-directed behavior and cognitive control. However, abnormal reductions in beta activity have been associated with poor cognitive performance and diminished executive functioning.

Overall, these findings suggest a shift in the balance of functional connectivity dynamics in AD, characterized by enhanced flexibility in slower oscillatory activity and more rigid, stereotyped dynamics in faster frequencies. This reorganization reflects both compensatory and pathological processes, providing further evidence of how AD affects the temporal architecture of large-scale brain networks.

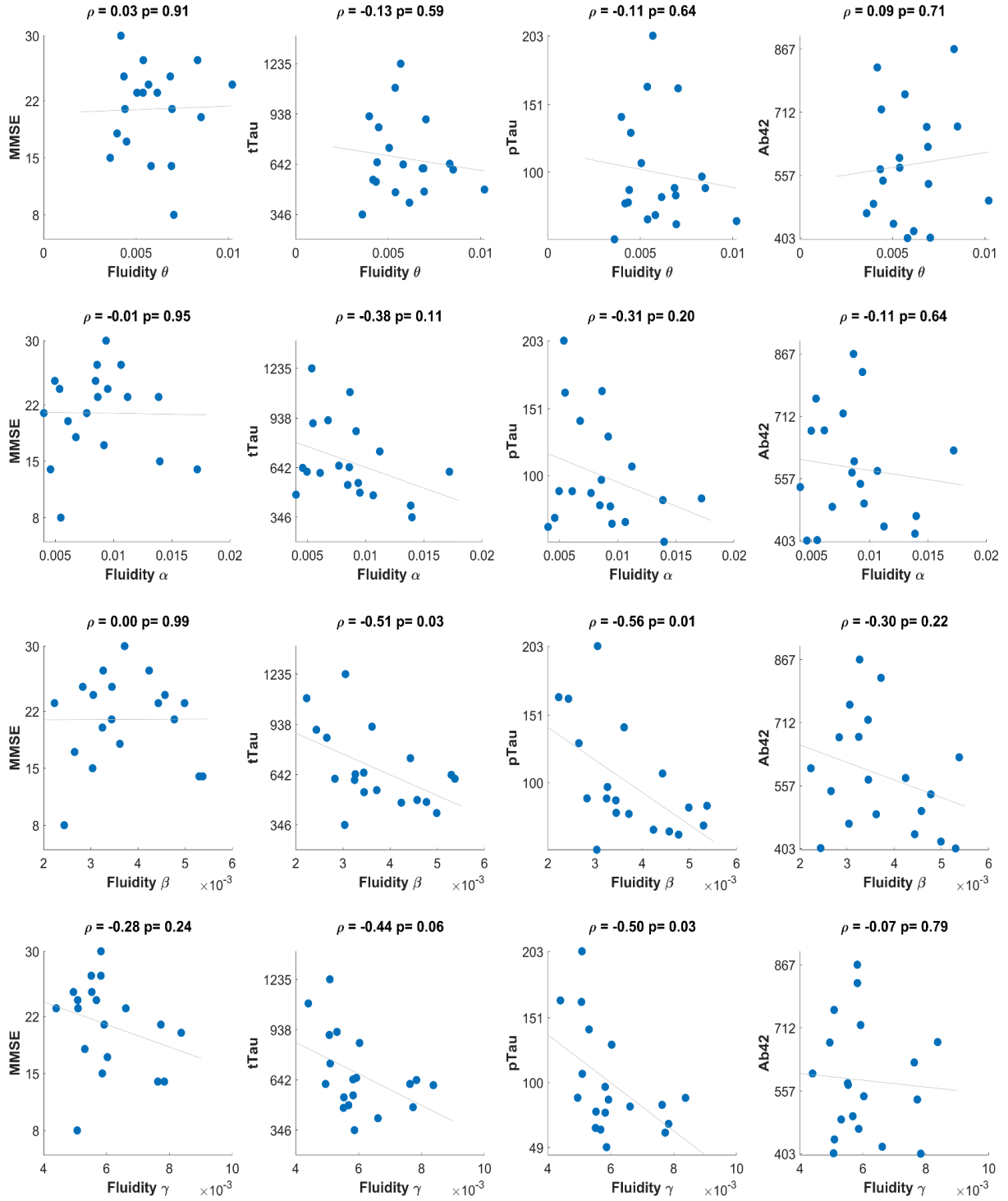


Figure 28. Fluidity in the β band qualifies as the best biomarker, noting significant anti-correlations with clinical measures in AD. Clinical measures in AD, namely MMSE score, total tau (tTau), phosphorylated tau (pTau), and amyloid-beta 42 (Ab42) were compared against fluidity values in the four canonical bands (θ , α , β , and γ). The fluidity in β and γ bands significantly anti-correlated with the levels of tTau and pTau, but the results corroborate the differences from control only with respect to the β band.

To better interpret these findings, we examined their relationship with key pathological biomarkers such as total tau (tTau), phosphorylated tau (pTau), and amyloid-beta (A β) with clinical measures, such as the Mini-Mental State Examination (MMSE) score.

Correlation analyses showed no significant associations between alpha/theta fluidity and clinical or biomarker measures. In contrast, beta/gamma fluidity exhibited a significant negative correlation with both tTau and pTau, while no relationship was found with A β levels (Figure 28). From a clinical perspective, these results suggest that the brain's capacity to maintain flexible dynamics, particularly at faster frequencies such as beta and gamma, is more closely linked to markers of cellular damage, as reflected by elevated tau protein levels in the cerebrospinal fluid. This pattern indicates that a reduced ability to switch efficiently between different dynamic states may be associated with tau-related neurodegenerative processes.

Given that beta-band fluidity showed a significant difference between Alzheimer's disease patients and healthy controls, and was also negatively correlated with t-tau and p-tau levels, the decision was made to focus subsequent analyses on beta fluidity. This measure appeared to be the most promising candidate among the explored features to serve as a potential biomarker of Alzheimer's disease. Using a multilinear regression framework, the study examined whether clinical disability, measured by the Mini-Mental State Examination (MMSE), could be predicted from a set of key variables: age, sex, tTau and p-Tau levels, and beta-band fluidity. This approach made it possible to evaluate the unique contribution of each predictor while taking into account the shared variance with the others.

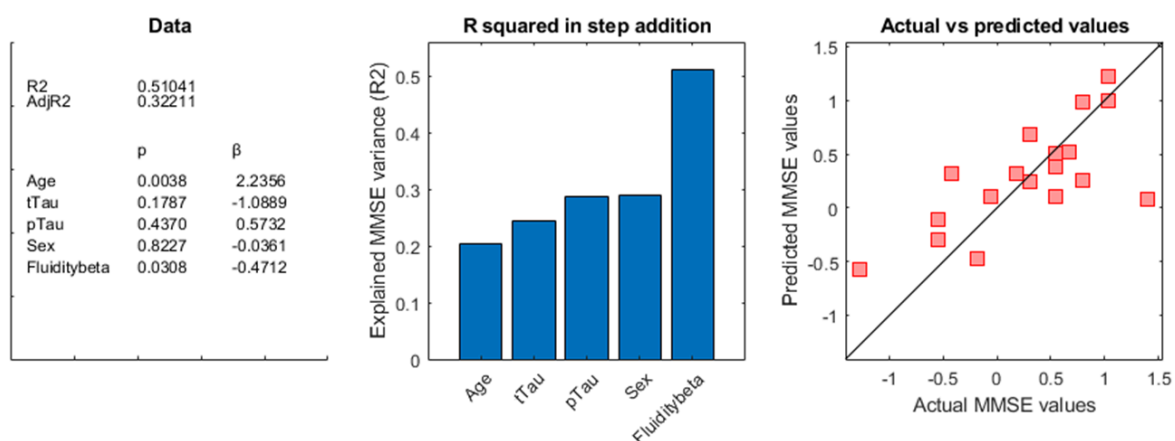


Figure 29: Predictive Power of Beta-Band Fluidity in Estimating Clinical Disability (MMSE). Comparison of the predictive performance (e.g., measured by R^2 or prediction error) of a multilinear regression model used to estimate Mini-Mental State Examination (MMSE) scores. The comparison is made between a baseline model incorporating only demographic and CSF biomarker data (Age, Sex, t-tau, p-tau) and the full model that additionally includes beta-band fluidity. The improved performance demonstrated when beta fluidity is included confirms its unique contribution as a potential biomarker in predicting clinical impairment in this cohort.

Including beta fluidity in the model improved its predictive performance (Figure 29). When all four predictors were considered together, the model explained 51% of the variance in MMSE scores ($R^2 = 0.51$; Adjusted $R^2 = 0.32$). The estimated contributions of each predictor were: age ($\beta = 2.2356$, $p = 0.0038$), tTau ($\beta = -1.0889$, $p = 0.1787$), pTau ($\beta = 0.5732$, $p = 0.4370$), sex ($\beta = -0.0361$, $p = 0.8227$), and beta fluidity ($\beta = -0.4712$, $p = 0.0308$).

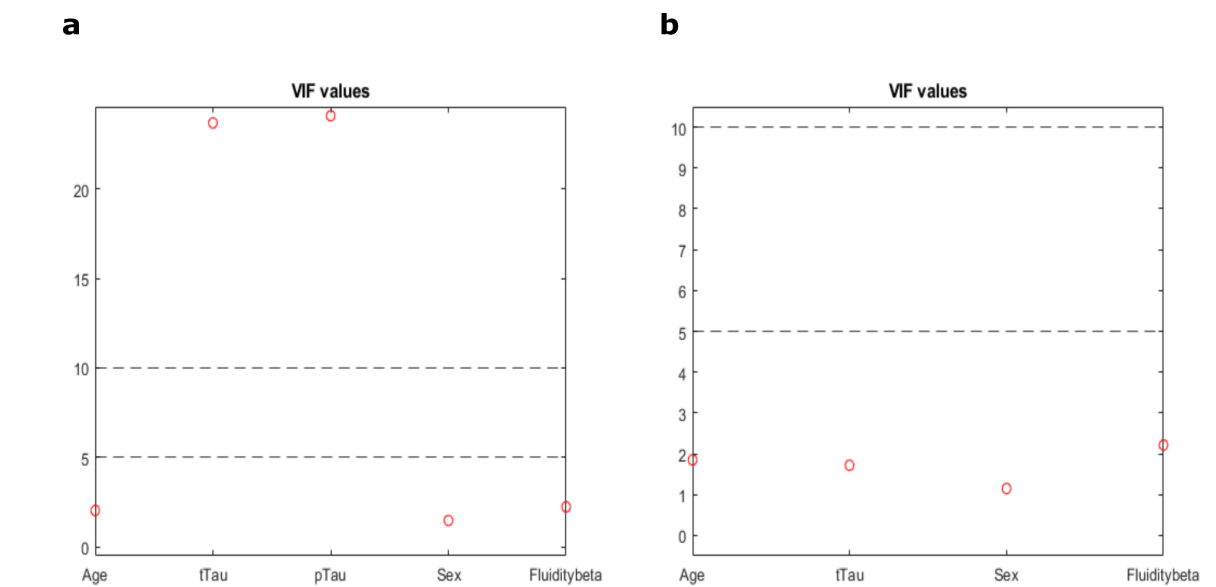


Figure 30: Multicollinearity Assessment via Variance Inflation Factor (VIF). Variance Inflation Factor (VIF) calculated for each predictor variable included in the multilinear regression model (e.g., Age, Sex, t-tau, p-tau, β -Fluidity). The horizontal line indicates the conventional threshold for problematic multicollinearity (e.g., $VIF > 5$ or 10). The high VIF calculated for phosphorylated tau (pTau), which exceeded this threshold, necessitated its exclusion from the final model to ensure stable and interpretable regression coefficients, due to its strong biological correlation with total tau (tTau).

However, phosphorylated tau (pTau) was excluded due to high Variance Inflation Factor (VIF) values exceeding the accepted multicollinearity threshold (Figure 30). VIF is a measure of how strongly a predictor is linearly related to other predictors in the model. High values indicate redundancy between variables, which can inflate standard errors, reduce interpretability, and destabilize the regression coefficients. Because total tau (tTau) includes phosphorylated tau (pTau) as part of its total protein concentration, the two measures are innately correlated. This strong biological overlap naturally leads to high VIF values in the regression analysis. By excluding pTau, the remaining predictors were sufficiently independent, ensuring more reliable and interpretable estimates.

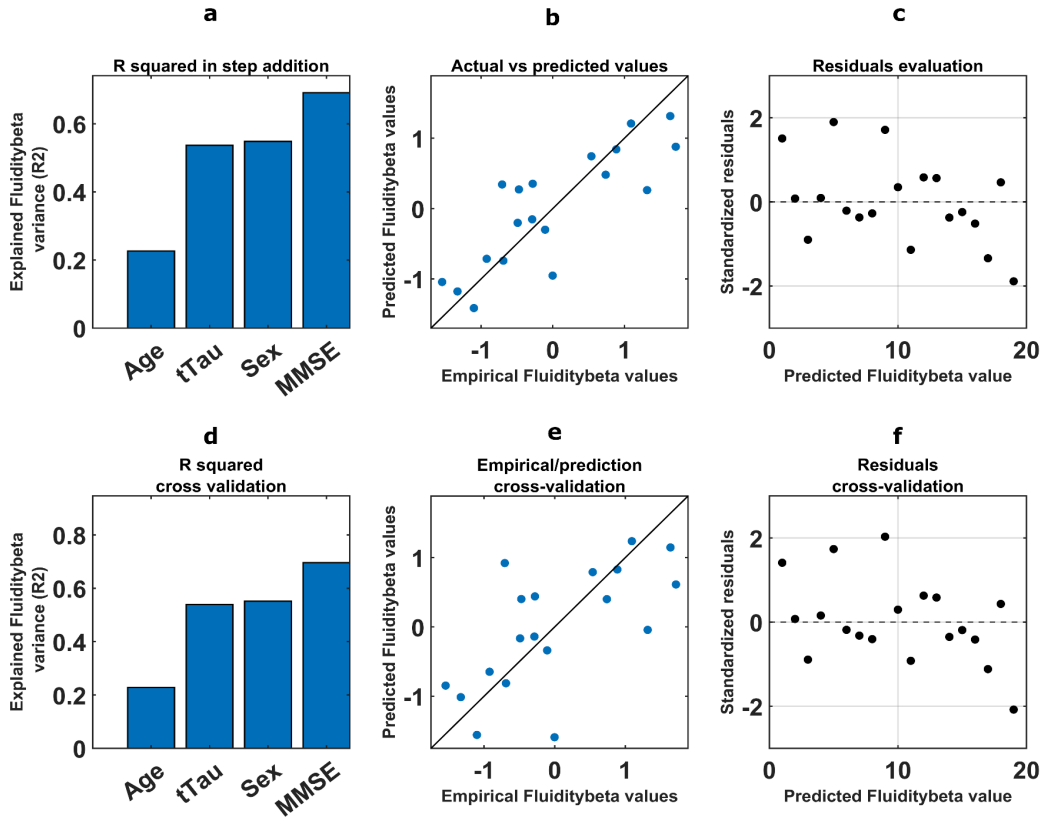


Figure 31: Predictive Utility and Stability of Beta-Band Fluidity in Estimating Cognitive Decline. Multilinear regression results predict MMSE scores using Age, Sex, t -tau, and beta-band fluidity (β -Fluidity). Panels (a) and (d) display the explained variance for the original model ($R^2=0.49$) and the Leave-One-Out Cross-Validation (LOOCV) model, respectively, confirming the unique contribution of β -Fluidity (which remained significant in both). Panels (b) and (e) show the close alignment between observed and predicted MMSE scores for the original and LOOCV models, while panels (c) and (f) present the corresponding residual analyses, validating the model's accuracy and generalizability across the cohort.

Despite p -tau being removed, considering all of the other predictors, the model explained 49% of the variance in MMSE scores ($R^2 = 0.49$; Adjusted $R^2 = 0.34$) (Figure 31). The estimated contributions of each predictor were: age ($\beta = 2.0829$, $p = 0.0037$), t Tau ($\beta = -0.4973$, $p = 0.0286$), sex ($\beta = -0.0956$, $p = 0.4990$), and beta fluidity ($\beta = -0.4868$, $p = 0.0232$). These findings indicate that beta fluidity adds meaningful explanatory power to the model, over and above the effects of demographic and pathological variables.

To verify the stability and generalizability of the model, a leave-one-out cross-validation (LOOCV) procedure was performed. In this validation strategy, one subject is systematically left out of the training set and used as the test case, repeating the procedure for all participants. The results from the cross-validated model closely mirrored those of the original analysis, with the explained variance remaining at 49% ($R^2 = 0.49$; Adjusted $R^2 = 0.34$). In this model, the contributions of the predictors were as follows: age ($\beta = 2.03$, $p = 0.0073$),

$t\tau$ ($\beta = -0.7017$, $\rho = 0.0387$), sex ($\beta = -0.1780$, $\rho = 0.5290$), and beta fluidity ($\beta = -0.6117$, $\rho = 0.0340$). As illustrated in Figure 31, the predicted MMSE scores showed a close match with the observed values (panels b and e), and the residual analysis (panels c and f) supported the accuracy of the model's fit. The gain in explained variance reinforces the clinical significance of beta fluidity as a meaningful correlate of cognitive decline in Alzheimer's disease.

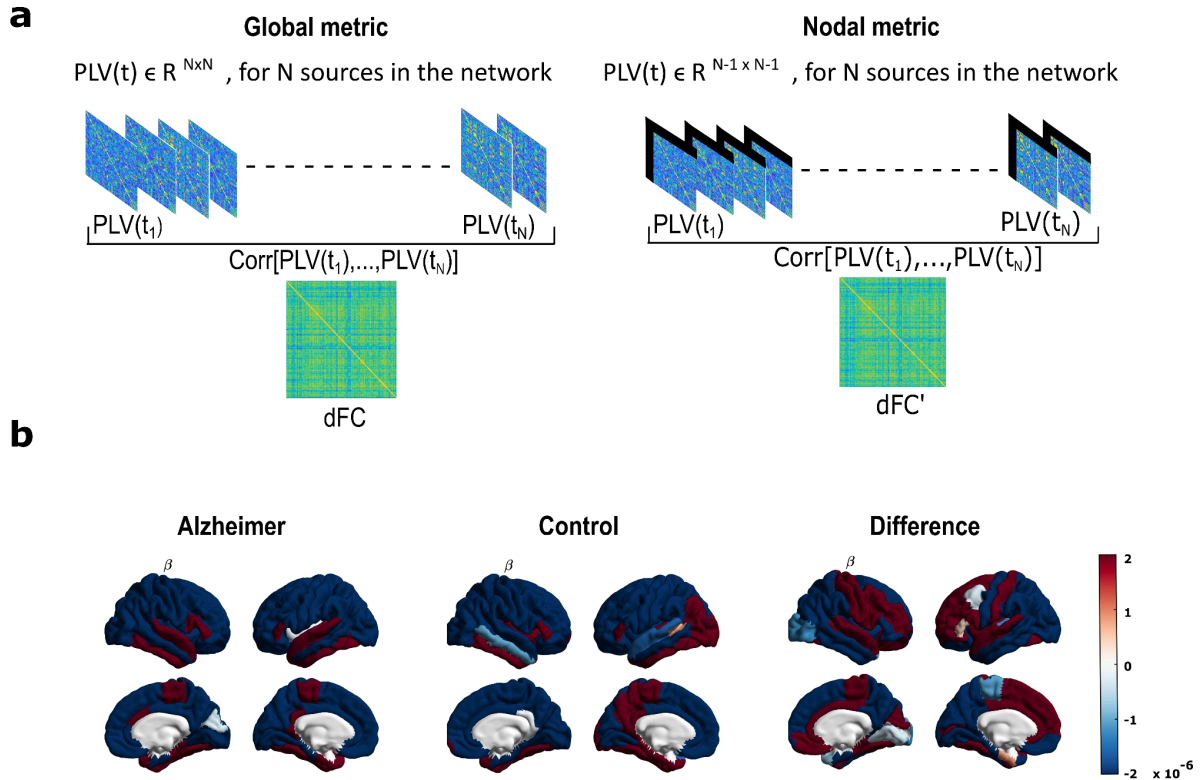


Figure 32: Regional Contribution to Global Beta-Band Fluidity. (a) The nodal approach employed to determine the relative impact of individual brain regions on overall global beta-band fluidity. The difference between the original global fluidity measure and the fluidity was calculated following iterative removal of regions one at a time. (b) Computed regional contributions mapped onto the brain surface for Alzheimer's Disease (left) patients, healthy controls (middle), and the group differences in regional contribution (right), respectively. In the left and middle panels, red regions represent important nodes whose removal causes a larger reduction in global fluidity, whereas blue regions indicate less important nodes whose removal has little or no effect. In the right panel, red regions denote nodes whose removal leads to a larger decrease in global fluidity in AD compared with controls, while blue regions indicate nodes whose removal produces a smaller effect. Blue regions likely contribute less to fluidity in AD due to their function being already impaired.

At this stage, after identifying a correlation between global beta fluidity and tau, the analysis focused on determining whether the observed alterations in fluidity were driven by specific brain regions rather than being uniformly distributed. Although EEG provides limited spatial resolution, the aim was to examine whether certain regions might exert a stronger influence on fluidity than others.

To achieve this, the investigation moved from a global measure of fluidity to a nodal, region-specific approach. The goal was to understand the role of individual brain regions in shaping overall fluidity, either by enhancing it or by constraining the brain's capacity to maintain it. For this reason, global fluidity was recalculated iteratively, removing one region at a time (Figure 32a). For each iteration, the difference between the original global fluidity and the value obtained after excluding a specific region was computed. This procedure yielded a measure of the relative contribution of each region to overall fluidity.

These regional contributions were then visualized on the brain surface for both Alzheimer's disease (AD) patients and healthy controls, as well as for the differences between the two groups (Figure 32b). The results indicated that certain regions, most notably those in the lower temporal lobe, had a disproportionately large influence on global beta fluidity in both groups. When these regions were removed, the reduction in beta fluidity was more pronounced, suggesting their central role in supporting dynamic network flexibility. Interestingly, temporal regions appeared to play an important role in both AD patients and controls, implying that they are core contributors to fluidity regardless of disease status.

When comparing AD patients and controls directly, however, no consistent spatial pattern emerged (Right panel in Figure 32b). The difference map reflects how the removal of each region differentially affects global fluidity in the two groups: positive values indicate a larger impact in controls, whereas negative values indicate a larger impact in AD patients. For instance, regions highlighted in red for AD suggest that removing these areas leads to a greater reduction in fluidity in patients, indicating a stronger contribution of those regions in the diseased brain. In contrast, blue regions appear to contribute less to fluidity in AD, possibly because their functional role is already compromised, resulting in minimal additional change when they are removed.

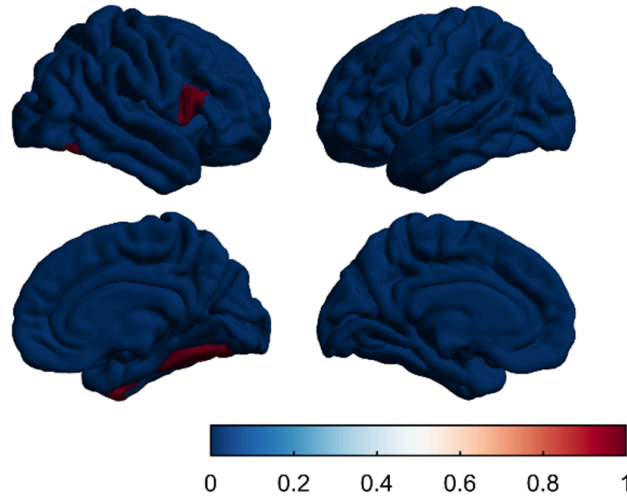


Figure 33. Permutation test of regional fluidity differences. Results of a permutation test performed to assess the statistical significance of the regional differences in the impact of region removal on global fluidity between AD patients and healthy Controls.

A permutation test was also conducted by randomly shuffling group labels to assess the statistical significance of the regional differences. Although two regions reached nominal significance, these effects did not survive correction for multiple comparisons (Fig.33).

3.9 Considerations

The fluidity in the beta band, as it can be measured precisely, rapidly, and reliably through non-invasive techniques such as EEG, represents a promising potential biomarker. Having a clear and reproducible feature provides a fundamental starting point to a working hypothesis that can be embodied into a computational whole-brain model.

Features play a crucial role in whole-brain modeling as they provide a quantitative and biologically meaningful target to calibrate the model against. They determine a specific model configuration from an infinitely vast parameter space that replicates an observable and measurable phenomenon. This ensures that the emerging dynamics faithfully reflect the underlying physiological or pathological mechanisms. This makes it possible not only to reproduce empirical data but also to explore alternative scenarios, test causal hypotheses, and evaluate simulated interventions.

The future goal is therefore to employ a whole-brain model of Alzheimer’s disease, using beta-band fluidity as the reference feature. This approach has already been adopted in the study of MS. In that case, the literature had already identified a characteristic feature of

macroscopic brain dynamics in MS: the shift of the spectral peak in the alpha band. This allowed the selection and design of a model capable of explaining and reproducing this disease mechanism. The details of the model construction will be explained in the next chapter. Equivalently, the intention now is to use beta-band fluidity to guide the model's architecture, enabling the investigation of how local and global alterations in brain connectivity may give rise to the observed pattern; thus opening the way to a mechanistic understanding of the pathophysiology of Alzheimer's disease.

4. Mapping Brain Lesions to Conduction Delays: The Next Step for Personalized Brain Models in Multiple Sclerosis

Multiple sclerosis (MS) is a complex autoimmune disease that affects the central nervous system. It damages the myelin sheath that surrounds axons, disrupting communication between different brain regions. When an action potential goes from a myelinated region to a bare stretch of demyelinated axon, it encounters a region of high membrane capacitance and reduced membrane resistance (63) (Figure 34). The inward current produced at the last healthy node may not be sufficient to generate the capacitive charge needed to bring the demyelinated section to threshold. Moreover, this local circuit current does not propagate as effectively as it normally would, because it faces a segment of axon with a shorter length constant resulting from its lower membrane resistance. These effects combine to slow or even block the conduction of action potentials, causing devastating effects. People with MS can experience a wide range of symptoms, from sensory or motor problems to visual disturbances, ataxia, or cognitive changes (140,141). The course of the disease is unpredictable, and its origin involves both genetic susceptibility and environmental factors, which together set off an abnormal immune response against myelin (141–144).

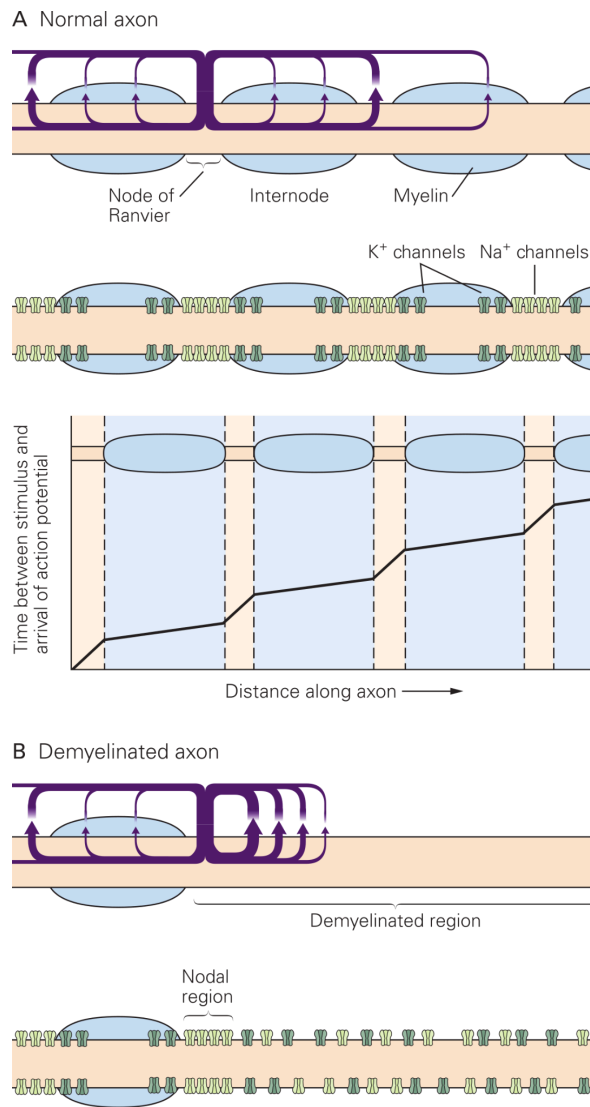


Figure 34. Action potentials in myelinated nerves. (a) Capacitive and ionic membrane current densities are substantially greater at the nodes of Ranvier compared to the myelin-insulated internodes (indicated by arrow thickness, representing current density per unit area). Due to the higher capacitance at the nodes, the action potential briefly decelerates before rapidly "skipping" to the next node during propagation (left to right). (b) Demyelination leads to slower or blocked action potential conduction. This occurs because local-circuit currents must charge a larger membrane capacitance, and the shorter length constant (resulting from reduced membrane resistance in the demyelinated area) impairs current spread down the axon.

As previously mentioned, the central problem in MS is the loss or alteration of myelin. When this structure breaks down, nerve conduction slows, and sometimes signals may even fail to arrive at the target (145–147). This slowing of communication is not just a local phenomenon: it affects how distant brain areas work together, which explains many of the clinical symptoms. The conduction velocity of action potentials is proportional to the degree of myelination (146). Therefore, the thickness of the myelin sheath, which is also closely associated with the axon diameter, plays a significant role in determining conduction velocity (148–150).

For decades, researchers have tried to capture these conduction delays, but the tools available were limited. Evoked potentials provide useful information about specific pathways, but can't give a full picture of the entire brain (151). In recent years, new approaches combining diffusion MRI with magnetoencephalography (MEG) have taken a stride forward in evaluating conduction delays and velocity (152,153). These methods use information about white matter microstructure, such as axon diameter and myelin content, together with electrophysiological recordings, to infer how signals are delayed as they travel through the brain. However, there are still important limitations, such as the resolution of MRI, which can reduce the ability to accurately measure microstructural parameters.

Still, a key question remains unanswered: how does the specific arrangement of lesions actually translate into delayed signal propagation? Patients who share a similar lesion volume can end up with very different clinical profiles. This mismatch suggests that the location and distribution of lesions may play a decisive role, perhaps even more than their total amount. Understanding this mapping could help explain why symptoms can look so different from one person to another.

Personalized whole-brain modeling provides distinct benefits for investigating such questions. Fundamentally, the mechanism of the underlying phenomenon can be studied by quantifying the influence of candidate biophysical parameters on large-scale cortical dynamics. Each brain region can be treated as a node, which subjects this influence to a network effect, mimicking the intractable brain network architecture. Furthermore, personalized models are tailored to the individual's anatomy and physiology, allowing us to explore how pathology in specific networks translates into changes in neural communication. Subtle differences, that are often hidden in group-averages, can be revealed. Thus, unlike group-level approaches, personalized MS whole brain models can account for the unique lesion patterns and connectivity architecture of each patient to realistically simulate pathological brain activity

In this study, we combined empirical measures from individual tractography and resting-state MEG recordings with whole-brain modeling and Bayesian inference to link structural damage with functional slowing in the brain's communication network. The main idea is to move beyond lesion counting and capture how structural damage reshapes the temporal dynamics of neural communication across the network.

The following analysis shows that the parameter reflecting lesion-driven conduction delays (γ) closely pertains to a characteristic feature of MS, namely, shifts in the alpha peak observed in empirical MEG data. This relationship was not simply a reflection of total lesion volume; instead, it carried independent and clinically meaningful information, showing a clear link with disability levels.

Altogether, these findings point toward a more functional and individualized understanding of demyelinating damage. Rather than treating lesions as static anatomical markers, this approach captures their dynamic impact on brain communication, offering a path toward more personalized models of MS. A schematic representation of the approach used is shown in Figure 35.

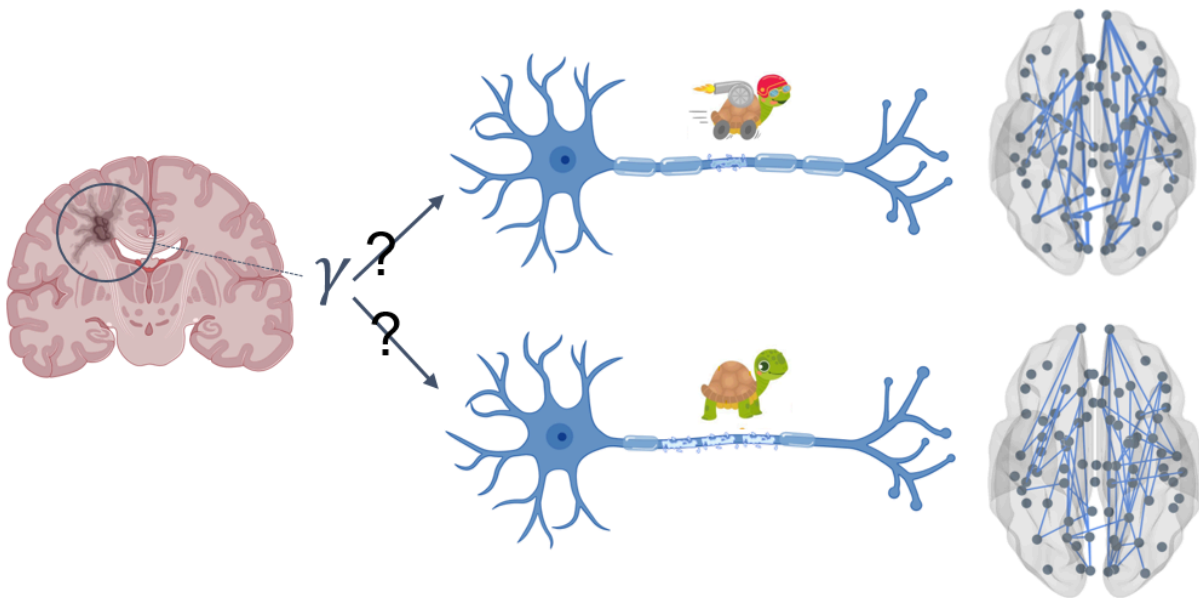


Figure 35. Whole-brain modeling admits personalized structural information to mechanistically simulate realistic brain activity. From left to right: schematic of a white matter tract lesion in MS. This information is compressed into the parameter γ , which captures the relationship between the structural lesion and the conduction velocity slowing of the nervous signal. On the top, γ takes a lower value as the lesion is not as severe (represented by a faster-conducting signal), compared to the bottom diagram, where a severe lesion translates into a higher value of γ (represented by slower-conducting signal). Eventually, γ is expected to determine the simulation's output and give rise to comparable features between these two cases.

4.1 Cohort details

The study involved both people with multiple sclerosis (MS) and healthy controls. All patients came from the outpatient clinic of the Hermitage Capodimonte Institute in Naples, Italy. Diagnosis was based on the 2017 McDonald criteria. Individuals under the age of 18, those who had experienced a relapse or received steroid treatment within the previous three months, and those with other neurological or psychiatric conditions that could interfere with

the results were excluded from the study. Every patient went through a full neurological exam. We also collected standard clinical scores, including the Expanded Disability Status Scale (EDSS), along with other cognitive and fatigue measures. Healthy controls were mostly caregivers and partners of the patients, so they matched well in terms of age and education. All participants gave informed consent, and the local ethics committee approved the study. Below is a table summarizing the characteristics of the patients (Table 2).

	Controls	MS	p-value
Age (years)	45.8 ($\pm$ 11)	44.9 ($\pm$ 9.9)	0.8
Education (years)	13.6 ($\pm$ 3.8)	13.8 ($\pm$ 5)	0.9
Gender (m/f)	6/14	6/12	0.3
Disease duration (months)	–	187.7 ($\pm$ 131.8)	–
EDSS	–	4.5 ($\pm$ 1.9)	–
SDMT	–	40.3 ($\pm$ 13)	–
FSS	–	36.1 ($\pm$ 14)	–
BDI	–	12.8 ($\pm$ 1.3)	–
LL	–	12.959 ($\pm$ 12.253) mm ³	–

Table 2. MS cohort features. DSS, Expanded Disability Status Scale; SDMT, Symbol Digit Modalities; FSS, Fatigue Severity Scale; BDI Beck Depression Inventory; LL, lesion load.

4.2 MRI Acquisition and Processing

The MRI data were collected and analyzed following the general framework described by Sorrentino et al. (2022) (14). In short, all scans were acquired using a 1.5 Tesla system (Signa, GE Healthcare). Diffusion-weighted images were obtained through an echo-planar imaging (EPI) sequence, while 3D-FLAIR scans were used to detect and segment white matter lesions. The preprocessing of the diffusion data involved several key steps aimed at improving the quality and reliability of the signal. Head motion and eddy current distortions were first corrected with dedicated tools available in the FMRIB Software Library (FSL). These corrections are important to ensure that the resulting diffusion maps are properly aligned and not distorted by movements during the scan. A brain mask was then generated from the B0 image using the Brain Extraction Tool to exclude non-brain tissue from further processing. After this, a diffusion tensor model was fitted at the voxel level, which enabled the estimation of water diffusion properties and anisotropy throughout the white matter. Fiber pathways were reconstructed using the FACT algorithm, providing a subject-specific representation of major white matter connections. The cortical Region Of Interest (ROIs) used in the analyses were derived from the Desikan–Killiany–Tourville (DKT) atlas. White

matter lesions were segmented from the 3D-FLAIR scans using the lesion prediction algorithm included in the Lesion Segmentation Tool (LST v3.0.0; www.statistical-modeling.de/lst.html) within SPM. Once generated, the lesion maps were coregistered to the EPI images of the same participant, following the procedure introduced by Ashburner and Friston (1997) (154). This alignment step ensures that all imaging modalities are expressed in a shared anatomical space. The transformation matrix obtained during this process was then applied to the lesion masks so that the spatial lesion information precisely matched the diffusion data. To maintain the accuracy of the lesion boundaries, the images were resampled using nearest-neighbor interpolation. Unlike other interpolation methods, this approach preserves sharp edges by directly transferring the original voxel values, which is particularly important when dealing with lesion volumes. The outcome was a set of lesion masks aligned with the DTI data on a per-patient basis, enabling integrated structural and lesion mapping for each subject. Finally, for every pair of ROIs, the mean tract length was computed along with the proportion of lesioned voxels intersected by those fibers. These calculations were performed using an in-house program written in Interactive Data Language (IDL). The tract length was estimated by summing the straight segments between successive turning points of each fiber and averaging across the entire bundle. This comprehensive processing pipeline provided a precise and individualized structural framework for each participant, laying the groundwork for investigating how lesion distribution influences white matter connectivity and, ultimately, neural communication across the brain.

4.3 MEG Preprocessing and Source Reconstruction

Each participant took part in a magnetoencephalography (MEG) recording session that included two eyes-closed resting-state recordings. In parallel, electrooculogram (EOG) and electrocardiogram (ECG) signals were collected to track and later remove physiological artifacts linked to blinking and cardiac activity. The MEG signal was sampled at 1024 Hz. Afterwards, a fourth-order Butterworth IIR filter with a passband between 0.5 and 48 Hz was applied to clean the recordings further.

The preprocessing and source reconstruction pipeline followed previously established protocols (130), and the analyses were conducted using the FieldTrip toolbox. Noise from external sources as well as physiological artifacts were identified and removed through independent component analysis (ICA). The source reconstruction procedures were carried out according to the approach detailed in Sorrentino et al. (2022) (14).

4.4 Model Selection and Design

The idea behind the modeling was simple in principle but powerful in practice: we wanted a whole-brain model that could capture how structural damage affects the timing of neural communication across the network. Malfunctional synchronization via neuronal oscillations was another primary suspect that had to be captured by the dynamics of the model. Adapting a Stuart-Landau oscillator for each cortical region encompassed both of these features. The network's oscillating frequency becomes subject to an emergent, macroscopic rhythm that imposes its dynamics on individualized region oscillations. Second, time lags have already been successfully integrated within its standard formalism (delayed differential equations) to allow for simulation of conduction delays (155).

Following the implementation from Cabral et al., 2022 (155), each oscillator had a natural frequency around 40 Hz (ω_j) and its dynamics were configured to dampening oscillations ($\alpha = -5$). Their coupling function was scaled by each participant's structural connectome obtained from DTI. The strength of the connections was determined by the subject-specific DTI fiber counts (c_{jk}), and signal propagation between regions included a time delay term (τ_{jk}). The neural activity of each region is represented by the following equation:

$$\dot{Z}_j = Z_j \left(\alpha + i\omega_j - |Z_j|^2 \right) + G \sum_{j \neq k}^N c_{jk} \left[Z_k(t - \tau_{jk}) - Z_j(t) \right] + \beta \left(\eta_1^j + i\eta_2^j \right)$$

Where:

$$\tau_{jk} = \frac{d_{jk}}{v_{jk}} + \gamma \cdot l_{jk}$$

We propose a linear formulation to describe the relationship between the conduction delays and the amount of structural damage in each white matter tract. Indeed, the conduction delay τ_{jk} for each tract is calculated by dividing the Euclidean distance between two nodes (d_{jk}) by the conduction velocity (v_{jk}) and adding a term that accounts for lesion-related delay ($\gamma \cdot l_{jk}$); where l_{jk} is a personalized measure of the edge-specific lesion amount and the γ parameter represents the intensity of the influence of the lesions on the delay. The lesion contribution l_{jk} was estimated from the percentage of lesioned voxels per tract. Simply, the more damage a tract sustained, the longer it took for the signal to arrive. This term was not taken into consideration in Sorrentino et al., 2023 (156), which was treated as a reference to our implementation. The parameter G reflects the overall strength of communication within the network, scaling the anatomical links between brain regions coming from the empirical and

individualized structural connectivity matrices. The time evolution of the dynamics was noise-driven as $\beta \left(\eta_1^j + i\eta_2^j \right)$ was nonzero ($\beta=1$). This is important in order to simulate resting-state conditions. This modeling framework gave us a direct way to link lesion topography to network-level temporal dynamics. By incorporating delayed differential equations, the model captures the effect of reduced signal propagation velocities, leading to phase shifts that enable the emergence of collective oscillations. As a result, the oscillators transiently synchronize in a metastable manner, locking into coherent states and giving rise to macroscopic rhythms different from the original natural frequencies of the individual units. The G parameter, together with the conduction velocities, v_{jk} , determine α -band oscillations in Z (156), slowing the system's collective dynamics relative to the single-node frequency.

4.5 Model Inversion

This whole-brain model setup delegated the γ parameter as the target parameter whose sensitivity to alpha peak shifts, robustly observed in MEG data of MS patients, had to be examined. Instead of using classical likelihood-based methods, which are often too computationally heavy for complex systems, we relied on a simulation-based inference (SBI) approach.

As said previously (see Introduction), SBI lets us infer model parameters without having to compute the likelihood function explicitly. A multitude of simulations is performed within a plausible range of the parameters under question, and a target set of features is subsequently computed. Then, a neural network is trained to learn the mapping between those features and the underlying parameters. Finally, empirical data features are used to sample from the learned posterior distribution of our target parameters.

The target parameter, γ , controls how strongly the lesions in a tract affect the conduction delays along that edge. We therefore simulated the 5,000 Stuart-Landau model ($n = 5000$) using samples drawn from a uniform prior distribution of γ . For each simulation, we computed a set of spectral features that summarized the dynamics of the model:

- Power spectra peak
- Amplitude of the power spectra peak

- Alpha band area-under-the-curve

While seemingly simple, the abovementioned features effectively capture the most relevant changes associated with conduction delays.

4.6 Results

The first step of the analysis was to confirm the presence of a shift in the alpha frequency peak and a reduction in alpha band (8-13 Hz) power spectra in 18 MS patients compared to 20 controls, as previously shown in the literature (156).

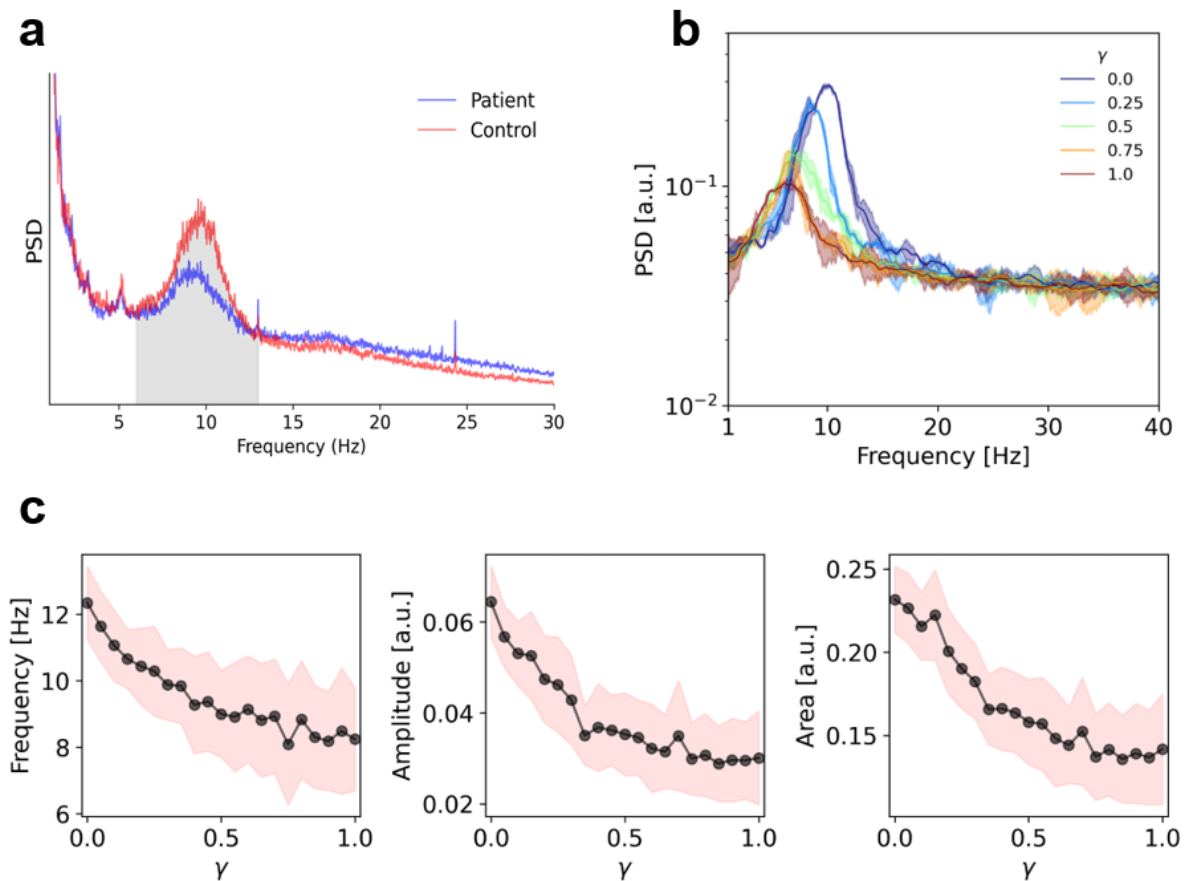


Figure 36. The γ parameter determines features of alpha band activity. (a) Empirical median power spectral density (PSD) across controls (red) and MS patients (blue). (b) Simulated PSD for increasing γ values shows a decreased peak in the alpha band. Mean/standard deviations across different simulations for each γ value are represented with full lines/shades. (c) Left to right: peak frequency, amplitude of peak frequency, and area under the PSD in the alpha band with respect to increasing γ values. The shaded area corresponds to $\pm$ one standard deviation from the mean value for each frequency.

Figure 36 shows the group-level PSD for patients and controls: as we can see, MS patients exhibit a decreased power within the alpha frequency band as compared to the healthy group. To make sure fatigue wasn't driving this effect, we also looked at the theta/alpha ratio, a

common proxy for tiredness (157,158). The ratio didn't differ significantly between groups, suggesting that the observed spectral differences were not simply due to fatigue.

Next, we mapped the spatial distribution of the lesions across white matter tracts. For each subject, we binarized the lesion masks at the edge level, meaning we checked whether each tract was affected or not (Figure 37b). From this, we calculated nodal degrees to see which regions were most connected to lesioned edges (Figure 37a).

In most patients, lesions clustered in specific pathways, while other areas remained relatively preserved. This uneven topography was important as it suggested that even patients with similar total lesion volumes might have very different network-level effects depending on which tracts were involved.

We also summed the binarized lesion masks across participants to get a sense of common patterns. Some tracts were frequently affected across the cohort, while others were rarely damaged (Figure 37 c).

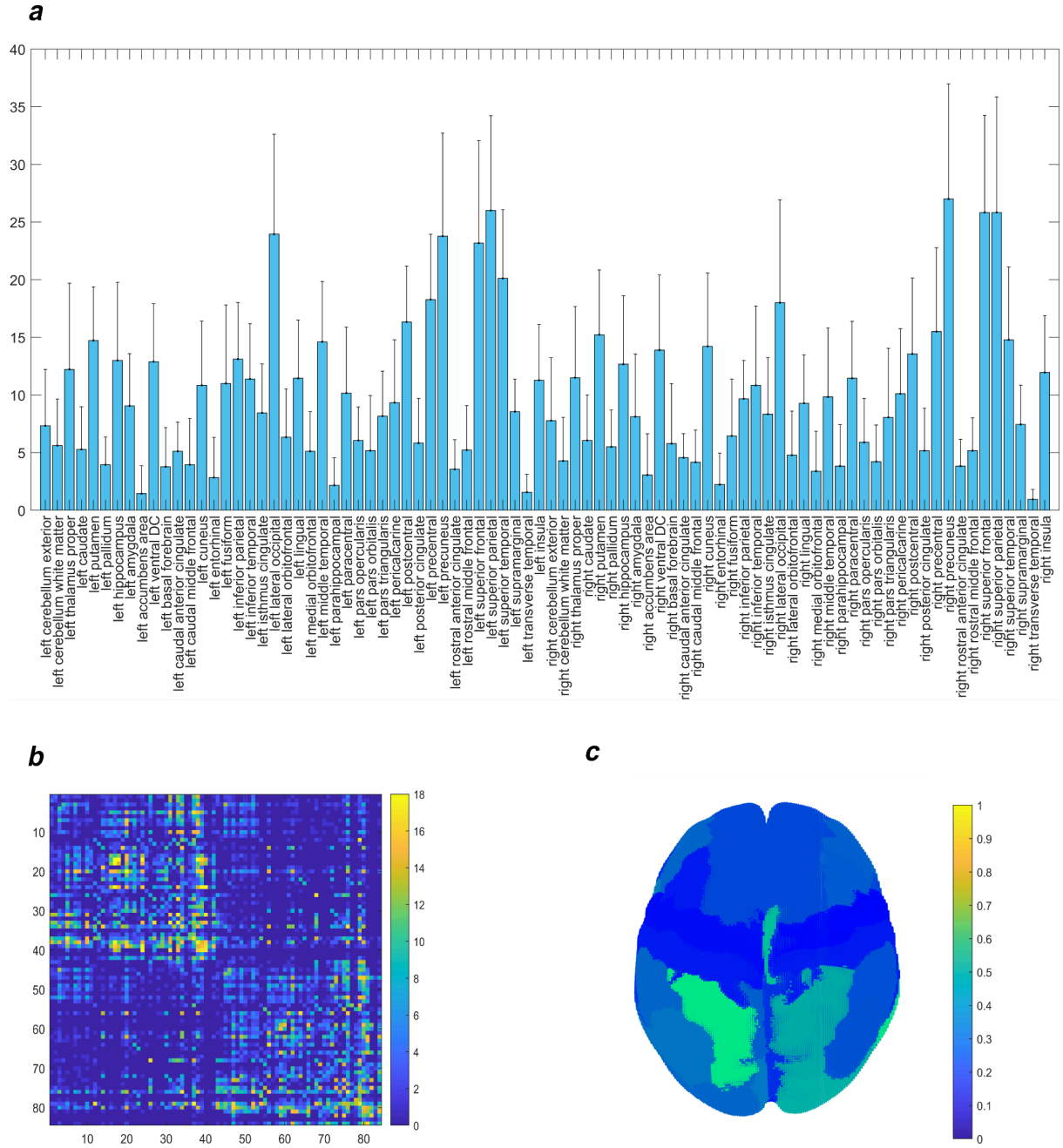


Figure 37. Detailed Anatomical Ljk Networks. (a) Count of lesioned tracts originating from each region; (b) Matrix representation of lesion severity across individual tracts. Each element represents the degree of structural damage between a pair of brain regions. Higher values (yellow) indicate tracts with greater lesion severity, whereas lower values (blue) correspond to relatively preserved connections. (c) Regions ranked by the average severity of lesion impact across patients. Higher values (yellow) indicate regions with the highest lesion load.

We then went back to the model to see how these structural lesions translated into changes in the simulated power spectrum. By increasing the γ parameter (which represents the strength of the lesion effect on conduction delays), we observed a progressive reduction of the amplitude of the alpha peak in the spectrum and a shift in its frequency. In other words, the

more weight we assigned to the lesions, the greater impact on conduction delays we had and the more the simulated brain activity resembled what we saw in patients.

Simulated spectra change as γ increases, quantified through peak frequency, peak amplitude, and area under the PSD curve all decreasing with higher γ values (Figure 36b,c).

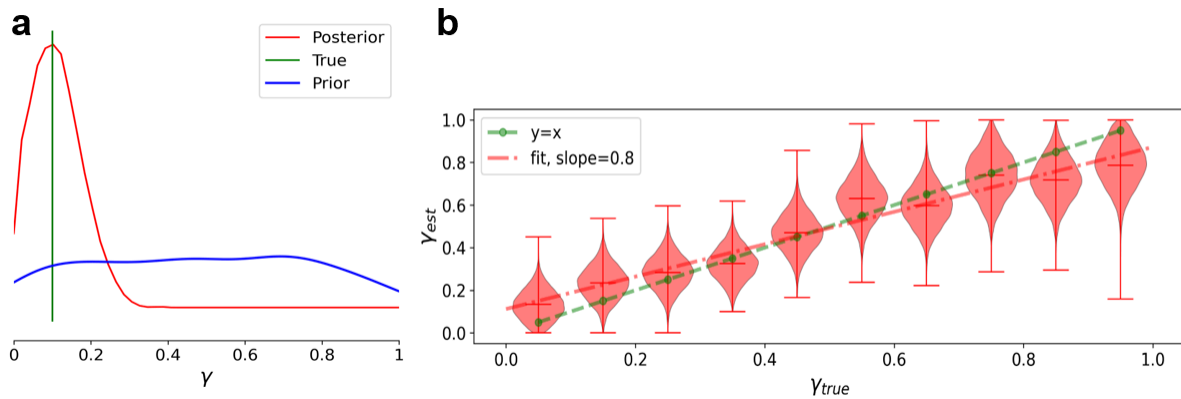


Figure 38. Synthetic validation of SBI for different model configurations over the parameter γ . (a) SBI converged to a posterior distribution that peaked at the ground truth of the parameter γ , while the prior corresponded to a uniform distribution from 0 to 1. (b) Same test, but for a larger range of γ values. The dashed red line and the green line correspond to linear regressions on the mean values of the estimated posteriors and ground truth values, respectively. The slope reflects the accuracy and consistency of the model inversion for the different γ values.

Then we used SBI to estimate the parameter γ using PSD features. Prior to any sampling via empirical observations, we validated the robustness of the inference process of SBI using different synthetic model configurations (posterior predictive checks) over the parameter γ (Figure 38). Simply put, before applying the inference procedure to real data, we checked if the SBI pipeline worked properly on synthetic data. Using simulated datasets with known γ values, we were able to accurately recover the true parameter values. The posterior distributions estimated by SBI match closely with the ground-truth values, and exhibited a significant shrinkage compared to the prior distribution (red vs green curves, and the blue distribution shown in Figure 38a, respectively). The violin plots in Figure 38b illustrate the estimated posterior distributions obtained by varying the parameter γ , with the regression line (dashed red lines) closely following the ground truth (green line). This confirmed that our inference model could reliably estimate γ across model configurations.

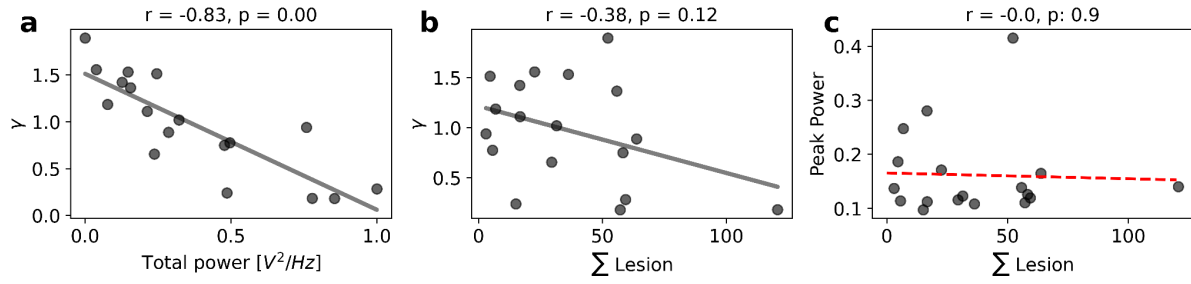


Figure 39. The lesion-specific γ parameter strongly correlates with the alpha band peak power irrespective of the total number of lesions. (a) Strong negative correlation between the γ metric and the power in the alpha band ($r = -0.83$, $p = 0.00$), suggesting that higher γ values are associated with a significant decrease in alpha power (normalized across subjects between 0 and 1). (b) The correlation between the γ metric and the anatomical lesion load was also negative but non-significant ($r = -0.38$, $p = 0.12$). (c) No correlation was noted between the empirical peak frequency and lesion load ($r = 0.00$, $p = 0.9$), indicating independence from the measured structural damage.

With the robustness of our inference pipeline validated synthetically, we moved on to estimate γ from our empirical MEG data. We extracted the same spectral features from each participant's power spectrum and fed them into the trained SBI network. The output was the posterior distribution of γ for each subject, which effectively told us how much the lesions were slowing conduction in that individual. This inversion step was crucial: it allowed us to move from static lesion maps to functional, personalized estimates of conduction delays, without the need to directly measure them experimentally.

The gamma parameter we estimated showed a strong negative correlation with the alpha peak in the brain's activity ($r = -0.83$, $p < 0.001$) (Figure 39a). Interestingly, the most probable gamma value for each subject was inversely proportional to the observed alpha peaks, while these peaks did not correlate with the total lesion volume ($r = -0.38$, $p = 0.12$) (Figure 39b). This demonstrates how the specific locations of myelin lesions affect conduction delays in the brain. Indeed, the parameter γ in each patient weighs a different set of edges (that is, those who are lesioned in that patient). Moreover, as we expected, there is no correlation between the total lesion volume and the alpha peak frequency (Fig. 39c).

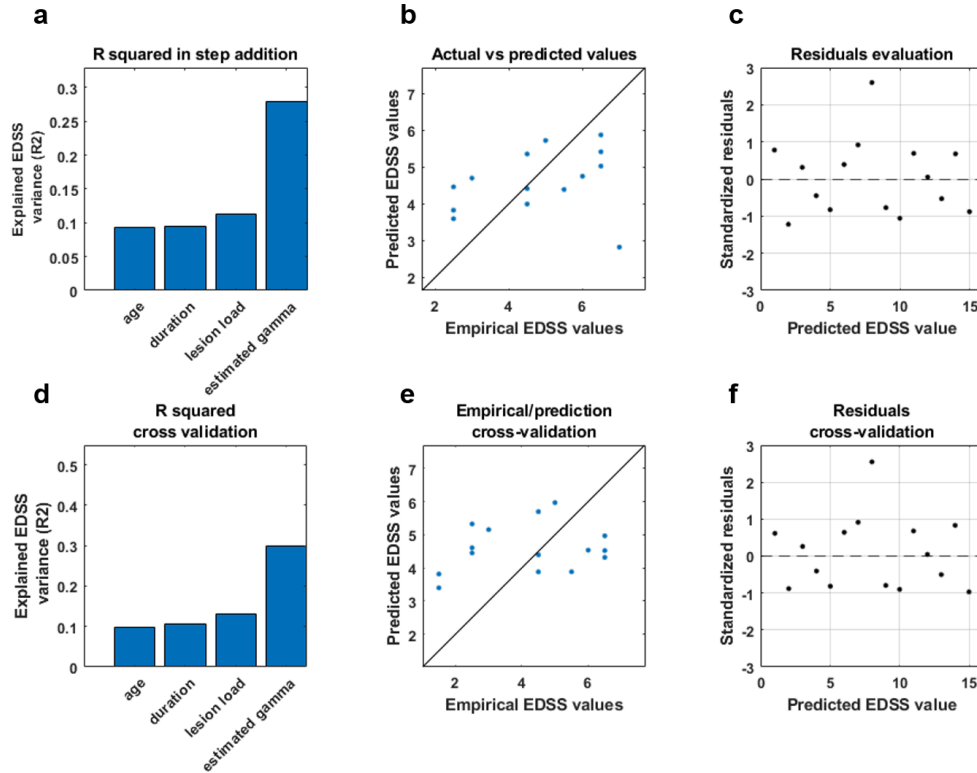


Figure 40. The parameter γ enhances clinical outcome prediction. (a–d) Variance explained by the model adding 4 predictors: age, duration, lesion load, and estimated γ . The parameter γ enhances prediction accuracy in both classical multilinear ($R^2 = 0.2793$; $AdjR^2 = 0.017226$) (age $\beta = 0.0227$ $\rho = 0.7328$; duration $\beta = 0.0015$ $\rho = 0.7547$; lesion load $\beta = -0.0000$ $\rho = 0.5921$; γ $\beta = -3.3099$ $\rho = 0.1366$) and cross-validated models ($R^2 = 0.29882$; $AdjR^2 = 0.018348$) (age $\beta = 0.0327$ $\rho = 0.7229$; duration $\beta = 0.0011$ $\rho = 0.7421$; lesion load $\beta = 0.0000$ $\rho = 0.5968$; γ $\beta = -3.3972$ $\rho = 0.1784$). (b–e) Predicted versus empirical EDSS scores; (c–f) Residuals evaluation.

Finally, a multilinear regression model was built to test whether γ contributed to predicting disability, measured by the Expanded Disability Status Scale (EDSS) (Figure 40). We built a multilinear regression model including age, disease duration, total lesion volume, and γ .

Although the model did not reach statistical significance, adding γ increased the explained variance, indicating that the parameter has clinical relevance despite being non-predictive. Moreover, it is evident that the total lesion load has less predictive power.

This is the first study showing how specific locations of myelin lesions influence conduction delays in the brain. Our findings emphasize the relevance of lesion topography in predicting clinical outcomes in MS patients and underlie the importance of employing personalized whole-brain models for a more accurate characterization of disease effects.

5. Discussion

Spatial navigation is a cognitive function heavily dependent on the hippocampal formation, particularly on the network of place cells (66,94,159). Place cells are hippocampal neurons that become selectively active when an animal is in a specific location, effectively forming an internal cognitive map of the environment. In rodents and other mammals, different cell types in the hippocampal–entorhinal circuit (including place cells, grid cells, and boundary cells) cooperate to encode spatial information, enabling orientation and navigation in the environment (74,76–79). Interestingly, spatially tuned neurons, with properties analogous to place cells, have also been identified in non-mammalian species, such as zebrafish, in the telencephalon (160). Given that Alzheimer’s disease (AD) often manifests with early impairments in spatial orientation and navigation (161–163), understanding the normal mechanisms of place cell function is not only of fundamental interest but also clinically relevant. The disruption of these spatial coding mechanisms may underlie the navigational deficits observed in AD patients, who frequently become disoriented even in familiar settings. Therefore, developing detailed computational models of place cells under healthy conditions provides a mechanistic characterization of the pathophysiological processes (i.e., like those in AD) leading to impaired spatial cognition.

In this work, we first introduced a biophysically grounded model to investigate the cellular and synaptic mechanisms through which a hippocampal CA1 pyramidal neuron becomes a place cell. This model was inspired by experimental findings showing that place cell firing can be triggered by the convergence of two inputs: a distal input from the entorhinal cortex (EC) and a proximal input from the CA3, the Schaffer collaterals (SCs). Based on these experimental results, the model simulates the mechanisms underlying the formation of a Place cell during spatial navigation in a novel environment. The EC input can be considered as conveying contextual or rewarding information (as it can be modulated by the dopaminergic input from the VTA, suggested by experimental studies (92,164–167)). The SCs encode environmental cues, conveying landmark-related information. Our findings show that only a well-timed interaction between these two independent and spatially distributed signals can induce a dendritic plateau potential, that is a prolonged calcium wave propagating along the entire neuron. Crucially, our model shows that this dendritic plateau acts as a gating or instructive signal for plasticity: it marks a time window during which any active proximal synapses (from the CA3 inputs coding for specific environmental cues) will undergo synaptic potentiation. In other words, only the subset of Schaffer collateral synapses that were active

around the time of the plateau, presumably those representing the cues in the animal's field of view at a particular location, will be strengthened.

Through this process, a formerly "silent" or non-specific neuron can become tuned to a particular combination of sensory cues and location, thus turning into a place cell. Once the place cell is established, the neuron will fire reliably whenever the animal encounters the same cue or location again, even if the environment is rotated (as expected by experimental results (95)). A key insight from our model is the importance of the spatio-temporal separation of inputs in creating a robust and flexible place field, that is the area where the place cell fires. The proximal (CA3) and distal (EC) inputs carry independent information and target different dendritic compartments of the CA1 neuron. In our simulations, simply increasing the proximal synaptic drive (e.g., by visual cues alone) was not sufficient to make the neuron fire action potentials or become a place cell. It was the conjunction of this moderate proximal input with the appropriately timed distal plateau potential that led to local dendritic spikes but also to the induction of synaptic plasticity at the right place and time. This requirement effectively implements a coincidence detection mechanism: only when the animal is seeing a specific cue (activating a specific set of CA3 inputs) and some reinforcement/context signal occurs (triggering a plateau from EC input), those specific synapses will strengthen. Our results suggest that if such a mechanism is intact, a CA1 neuron can flexibly remap to encode new place fields corresponding to whichever environmental cue is paired with the plateau-triggering event. Over time, even the same neuron could potentially switch its place field to different locations as different cues become associated with rewarding or novel experiences, or contextual information. This flexibility is consistent with experimental findings indicating that CA1 neurons are not permanently dedicated to one place field but can remap under different conditions or tasks.

Notably, our model offers realistic biophysical simulations of place cells. Prior computational models of place cells often used simplistic neural networks, with two or more layers consisting of neuron-like elements (168,169). Others used pre-defined firing responses, for example, in some network models it is assumed that certain neurons fire when the animal is at a given distance/direction from a wall or object (170), or they used ad hoc plasticity rules to wire up place cells after exposure to an environment (171). While useful for theoretical explorations, such models do not explain how a real neuron's dendrites and synapses could achieve that tuning. In contrast, this biophysical model can capture the biology underlying this mechanism: it incorporates dendritic compartments and non-linear integration, capturing

the minimal set of biophysical elements that are needed for the plateau potentials and synaptic plasticity timing to occur.

This level of detail is sufficient to yield experimentally testable predictions, or it can be adapted to study pathological conditions. In a healthy scenario, as we modeled here, the interplay of EC and CA3 inputs produces robust place fields. If we introduce disease-related changes, we can simulate how place cell formation might fail or become unstable, potentially offering an explanation for why AD patients have spatial memory troubles. Indeed, one can hypothesize that AD pathology in the entorhinal-hippocampal circuit could impair the generation of dendritic plateau potentials or the downstream plasticity, thereby preventing stable place map formation, an interesting avenue that our model could help investigate by direct simulation. In summary, the place cell model lays a cellular-level foundation for understanding spatial cognition and its vulnerabilities: it shows that a precisely timed interaction of inputs is required for normal spatial learning, and it provides a template to explore how this process breaks down in disease.

While the hippocampal circuit provides a local mechanism for spatial coding, AD is characterized by widespread brain changes that go beyond the hippocampus. AD has been increasingly conceptualized as a network disorder or “disconnection syndrome”, in which cognitive decline arises from the breakdown of coordinated activity across the brain (121,122). To capture this aspect, we shifted our focus to large-scale brain dynamics.

Using EEG recordings, we quantified functional connectivity dynamics using a new metric called ‘fluidity’, which reflects the brain’s ability to dynamically adapt its activities over time (133). Conceptually, having a high fluidity means that the pattern of network connectivity is rapidly changing and exploring many configurations over time, whereas low fluidity means that the brain is stuck into more rigid, unchanging connectivity relationships. A healthy brain is thought to maintain a balance: it is stable to hold functional networks for efficient operation, yet flexible enough to adapt to new tasks or environmental demands (133).

Our results revealed a frequency-specific disruption of connectivity dynamics in AD. In the theta frequency band ($\sim 4\text{--}8$ Hz), AD patients showed increased fluidity compared to age-matched healthy controls, whereas in the beta band ($\sim 14\text{--}30$ Hz), they showed decreased fluidity.

Slower oscillations become hyper-flexible, implying that in AD patients there is an excessive and perhaps erratic fluctuation in the theta-band. The increased fluidity observed in the theta band may reflect instability or loss of the coordinated theta activities. Interestingly, we did not find a direct correlation between theta fluidity and cognitive test scores or AD biomarkers

(such as CSF amyloid or tau levels). This could mean that the theta dysregulated-dynamics are an early compensatory change (the brain trying to maintain function by flexibly engaging alternate pathways) or simply an epiphenomenon that does not directly drive cognitive symptoms. By contrast, faster oscillations become more stereotyped, i.e. “rigid”, meaning that beta oscillations in AD are abnormally stable. Unlike the theta-band fluidity, in the beta-band there is a clear association with the levels of tau protein in the CSF, a well-established marker of neuronal degeneration (172,173). Indeed, the beta-band fluidity significantly and negatively correlates with both total and phosphorylated tau protein levels. Furthermore, when considering cognitive performance (measured by the MMSE scores), beta fluidity emerged as a significant predictor, on top of other predictors. This result highlights beta-band fluidity as an important biomarker, particularly informative for understanding the relationship between network rigidity and cognitive decline.

Beta oscillations are generally linked to higher-order processes like executive function, attention, and sensory integration. A loss of fluidity in this band suggests that AD brains struggle to flexibly reconfigure these higher-order networks, perhaps leading to deficits in multitasking, attentional shifting, or other cognitive operations that require network adaptation.

The specific association with tau pathology aligns with the idea that tau-induced neuronal damage, such as synaptic loss and cortical atrophy, has a more direct impact on functional network integrity. Amyloid deposition, although an important diagnostic hallmark and utilized for diagnostic purposes (174,175), is not specific to neurodegeneration, nor to AD. (176–178). Thus, the beta fluidity measure might be used to complement disease monitoring, as it does not relate to beta-amyloid but specifically to tau-mediated neurodegeneration, which is more closely related to AD. As such, beta fluidity might constitute an effective non-invasive marker of disease progression.

These findings dovetail with a broader pattern observed in AD electrophysiology: a global shift towards slower brain activity, marked by decreased high-frequency activity and increased low-frequency activity (179).

The opposite changes we see in theta and beta fluidity could be two sides of the same coin, as the disease advances and neurons get disconnected followed by cell death, the brain may become less capable of sustaining fast oscillatory networks. Hence, beta networks become more stereotyped and consequently they may either fall back on, or become dominated by, slower oscillations (which then appear more erratic in turn). This, as mentioned before, is

consistent with previous works, indicating that the balance of communication shifts from higher to lower frequency activity as the disease progresses.

Importantly, traditional static functional connectivity analyses (such as Pearson correlation, Phase-locking value, coherence, etc.) in AD have often yielded inconsistent results (122,180–182), probably due to their inability to capture the temporal variability of network interactions and/or methodological differences. By examining the temporal variability of functional connectivity we add another layer of understanding: two patients might have similar average connectivity, but one might have highly variable connectivity over time (high fluidity) while the other is stuck in one pattern (low fluidity), which could relate differently to their cognitive status. Our work shows that incorporating the time domain reveals robust differences that align with disease markers and symptoms, offering a new perspective of AD as a disorder of network dynamics.

From a translational standpoint, the identification of beta-band fluidity as a sensitive metric of AD-related network dysfunction is promising: unlike molecular biomarkers (e.g., CSF tau or PET imaging), which require invasive procedures or expensive equipment (183), EEG-based measures are non-invasive, widely accessible, and cost-effective. If further validated, beta fluidity could serve as a biomarker for tracking AD progression or index treatment effects. Moreover, because fluidity captures a complex systems property of brain activity, it might change earlier than overt cognitive symptoms, making it a candidate for early detection, when interventions are most effective. Our findings indicate that incorporating beta fluidity alongside traditional factors improved the prediction of cognitive performance, hinting that these are neurophysiological alterations that are also relevant behaviorally. In sum, this study underscores that the breakdown of cognitive function in AD is not just a matter of losing neurons or regional atrophy, but essentially losing the dynamic coordination among those neurons. AD indeed appears to dismantle the brain's communication architecture and metrics like fluidity let us quantify the extent of that dismantling in specific frequency bands that are tied to cognitive operations.

Whereas AD primarily affects gray matter and cortical networks, multiple sclerosis (MS) is a disease that targets white matter connections through demyelinating lesions. Hence, this is a different set of pathophysiological alterations that also leads to changes in whole-brain dynamics and consequently to symptoms. In particular, MS patients experience a range of neurological symptoms, including cognitive changes. One well-documented effect of MS on brain function is a slowing of the brain's oscillatory activity, especially a reduction in the power and peak frequency of the alpha rhythm (8–13 Hz) (156,184–186). Healthy individuals

usually exhibit a dominant alpha peak frequency around 10 Hz, but MS patients often show a shift of this peak to lower frequencies alongside a drop in alpha power. This “alpha slowing” is thought to result from widespread longer conduction delays in neural signaling, presumably caused by demyelination (14,187).

In our work, we used a personalized whole-brain modeling approach for MS that could estimate a relationship between each patient’s unique distribution of white-matter lesions and the resulting conduction delays, through the changes observed in their MEG power spectrum. Rather than assigning arbitrary delays or altering global parameters uniformly, we wanted the model’s alterations to be directly informed by the MRI-visible lesions in the set of edges directly affected by the disease, which are patient-specific. To achieve this, we used simulation-based inference (SBI) methods to estimate a key parameter (γ) that represents the overall impact of a patient’s lesions on conduction velocity across the lesioned edges. Essentially, γ scales how much the model should slow down signaling along any lesioned neural tract.

The analysis revealed a clear negative correlation between the inferred γ and the alpha peak amplitude: patients whose lesion patterns led to a higher γ (meaning greater slowing) tended to have lower alpha power. This means that more severe (or “strategically” placed) demyelination results in a greater reduction in the alpha rhythm. Interestingly, we found that the total volume of lesions in the brain did not correlate well with alpha power. In other words, the effect on whole-brain dynamics is not just a function of the quantity of lesions, but of the specific pathways that they affect. This finding echoes previous suggestions that the network context matters for determining the effect of white-matter lesions. Gollo et al. (2018), for instance, highlighted that lesions in different network edges can have very different effects on global oscillatory activity, even if the overall lesion load is similar (188). Our results provide concrete support for this in the context of MS, underscoring that lesion topography is a crucial factor in determining functional impairment. As such, our approach might offer a bridge between structural damage and disability.

From a clinical perspective, such personalized models open the door to patient-tailored predictions. For example, if we know a patient’s lesion locations from MRI, our model (once calibrated) could predict how much their alpha rhythm should slow down or how their brain network efficiency might change. This could help the early detection of subclinical damage, flagging the need for closer monitoring or earlier intervention. Additionally, the model could be used to test hypotheses about disease progression or treatment: e.g., what if new lesions appear in a particular pathway – how much would that further slow the alpha peak and/or

disrupt cognitive functions? Such applications move towards the concept of a “virtual brain” for each patient, where computational modeling supports clinical decision-making.

It is important to acknowledge that our MS model, focused primarily on conduction delays due to demyelination, captures only one aspect of the disease’s multifaceted pathology. MS also involves inflammation, cortical demyelination, axonal loss, and neurodegeneration, which can independently affect neural dynamics (189–192). Our model does not explicitly include these factors, meaning it may underestimate or oversimplify the impact of MS in cases where significant gray-matter atrophy is present. Although the model has some constraints, it provides a valuable means to investigate MS pathophysiology.

In summary, this study demonstrates the value of personalized large-scale brain models. This personalization is crucial because MS is heterogeneous: two patients might have the same diagnosis and similar lesion volumes, but the network consequences can differ widely. Accommodating heterogeneity in personalized models may improve clinical management. The approach aligns with the broader trend in neurology toward precision medicine, where interventions are customized to the individual’s specific pathology and physiology. Recent work on virtual brain modeling for epilepsy and other brain disorders has shown that simulation-based inference can achieve such tailoring, improving predictions of outcomes and optimal treatments (52). Our work extends this framework to MS, in the attempt to achieve better personalization of large-scale models and, ultimately, better healthcare.

Although AD and MS affect the brain in very different ways, our investigations in these two conditions highlight a common theme: specific measurable features of brain activity can serve as bridges between empirical observations and computational models. In MS, it was the slowing of the alpha rhythm; in AD, our results reveal the alteration of beta-band fluidity. These features distill complex brain changes into quantifiable metrics. Crucially, they can be obtained non-invasively and they carry significant information about the underlying pathology and about cognitive outcomes. Thus, they form an ideal target for computational modeling: by adjusting model parameters to reproduce these features, we ensure that the model reflects the real physiological impact of the disease.

Spatial navigation, mediated by place cells and related circuits, is a domain where cellular-level mechanisms meet behavioral outcomes. In AD, the impairment of spatial navigation may well involve both microscopic disruptions (e.g., synaptic dysfunction in the hippocampal formation affecting place cell stability) and macroscopic ones (e.g., overall network desynchronization). The overarching goal for future research is to build a unifying model that connects these scales. For instance, one could envisage a whole-brain model of

AD that includes a detailed hippocampal module (perhaps employing a version of our place cell model to represent how spatial representations are formed) embedded within a larger network that captures the cortex-wide fluidity alterations. By using the beta-band fluidity as a reference feature for calibration, such a model would ensure that the global dynamics match what we observe in AD patients. Meanwhile, the hippocampal module could be used to simulate navigation tasks, allowing us to test how network-level changes translate into navigation errors or impaired memory encoding.

The strategy of using a specific feature to guide model development is reminiscent of the approach we took to model MS. There, the well-known alpha peak shift in MS served as a starting point. By replicating the alpha slowing, the model became predictive of a real phenomenon, which makes the testing of predictions possible. Likewise, by anchoring an AD model to the beta fluidity reduction, we ground the model in an empirically observed hallmark of AD dynamics. From that foundation, we can explore the space of possible causes: for instance, does beta fluidity drop because certain hub connections are lost? Or is it because excitation-inhibition balance in cortical microcircuits shifts, favoring slower rhythms? What factors lead to the reduction of beta-band fluidity? We can manipulate the model to see which manipulations can produce the pattern of high-theta/high-delta and low-beta/low gamma dynamics that we found in AD patients. This could help identify the key pathological drivers. It also provides a way to test interventions: what factors could instead prevent these changes? Which circuits or mechanisms should be targeted by a therapeutic intervention? By answering these questions *in silico*, we generate hypotheses that can then be tested in animal models or clinical trials.

It is worth noting that spatial navigation deficits are not a typical feature of MS, which primarily affects other domains, so the place cell mechanism is more directly pertinent to AD (and related disorders that involve the hippocampus). However, the cross-talk between the findings in AD and MS is fruitful from a methodological standpoint. Modelling MS taught us that personalization and feature-targeting in models can reveal patient-specific disease effects. The study of AD offers a clear target feature (beta fluidity) and also a clear affected cognitive domain (navigation) that can be quantitatively probed. Thus, combining the strengths of both studies, the envisioned next step is to create a personalized model of AD that can account for both network-level dynamics and behavioral-level outcomes. The insights from place cell modeling will inform how we represent hippocampal degradation in the AD model, while the insights from dynamic connectivity will inform how we represent cortical network disconnection.

Conclusion

This thesis brings together three lines of research - the cellular mechanisms of spatial coding, the network dynamics in Alzheimer's disease, and the structural-functional modeling in multiple sclerosis - into a cohesive narrative. Each line addresses brain function at different scales (micro to macro) and in different pathological contexts, yet they converge on the idea that understanding and quantifying brain dynamics is key to unlocking cognitive dysfunction. By maintaining a consistent modeling framework and focusing on identifiable features (place fields, fluidity, spectral shifts), we ensure that the models remain biologically interpretable and empirically grounded. Ultimately, the hope is that such models will not only deepen our understanding of how diseases like AD and MS perturb the brain, but also guide us towards interventions.

Bibliography

1. Westlin C, Theriault JE, Katsumi Y, Nieto-Castanon A, Kucyi A, Ruf SF, et al. Improving the study of brain-behavior relationships by revisiting basic assumptions. *Trends Cogn Sci*. 2023 Mar;27(3):246–57.
2. Scharfen HE, Memmert D. The model of the brain as a complex system: Interactions of physical, neural and mental states with neurocognitive functions. *Conscious Cogn*. 2024 Jul 1;122:103700.
3. Bassett DS, Sporns O. Network neuroscience. *Nat Neurosci*. 2017 Feb 23;20(3):353–64.
4. Lisman J. The challenge of understanding the brain: where we stand in 2015. *Neuron*. 2015 May 20;86(4):864–82.
5. Li Q, Calhoun VD, Pham TD, Iraj A. Exploring Nonlinear Dynamics In Brain Functionality Through Phase Portraits And Fuzzy Recurrence Plots. *bioRxiv*. 2024 Sep 25;2023.07.06.547922.
6. Friston K. The free-energy principle: a unified brain theory? *Nat Rev Neurosci*. 2010 Feb;11(2):127–38.
7. Friston K, Kilner J, Harrison L. A free energy principle for the brain. *J Physiol Paris*. 2006;100(1–3):70–87.
8. D’Angelo E, Wheeler-Kingshott CG. Modelling the brain: Elementary components to explain ensemble functions. *Riv Nuovo Cimento*. 2017 Jul 1;40(7):297–333.
9. Azarfar A, Calcini N, Huang C, Zeldenrust F, Celikel T. Neural coding: A single neuron’s perspective. *Neurosci Biobehav Rev*. 2018 Nov 1;94:238–47.
10. Einevoll GT, Kayser C, Logothetis NK, Panzeri S. Modelling and analysis of local field potentials for studying the function of cortical circuits. *Nat Rev Neurosci*. 2013 Nov;14(11):770–85.
11. György B. Windows on the Brain. [cited 2025 Oct 20]; Available from: <https://academic.oup.com/book/11166/chapter/159630514>
12. Song H, Park J, Rosenberg MD. Understanding cognitive processes across spatial scales of the brain. *Trends Cogn Sci*. 2025 Mar;29(3):282–94.
13. Bressler SL, Menon V. Large-scale brain networks in cognition: emerging methods and principles. *Trends Cogn Sci*. 2010 Jun;14(6):277–90.
14. Sorrentino P, Petkoski S, Sparaco M, Lopez ET, Signoriello E, Baseli F, et al. Whole-Brain Propagation Delays in Multiple Sclerosis, a Combined Tractography-Magnetoencephalography Study. *J Neurosci*. 2022 Nov 11;42(47):8807.
15. Stöber TM, Batulin D, Triesch J, Narayanan R, Jedlicka P. Degeneracy in epilepsy: multiple routes to hyperexcitable brain circuits and their repair. *Commun Biol*. 2023 May 3;6(1):479.

16. Naze S, Bernard C, Jirsa V. Computational Modeling of Seizure Dynamics Using Coupled Neuronal Networks: Factors Shaping Epileptiform Activity. *PLOS Comput Biol*. 2015 mag;11(5):e1004209.
17. Babiloni C, Del Percio C, Lizio R, Noce G, Cordone S, Lopez S, et al. Abnormalities of cortical neural synchronization mechanisms in patients with dementia due to Alzheimer's and Lewy body diseases: an EEG study. *Neurobiol Aging*. 2017 Jul;55:143–58.
18. D'Angelo E, Jirsa V. The quest for multiscale brain modeling. *Trends Neurosci*. 2022 Oct 1;45(10):777–90.
19. Deco G, Jirsa VK, Robinson PA, Breakspear M, Friston K. The Dynamic Brain: From Spiking Neurons to Neural Masses and Cortical Fields. *PLOS Comput Biol*. 2008 ago;4(8):e1000092.
20. Breakspear M. Dynamic models of large-scale brain activity. *Nat Neurosci*. 2017 Mar;20(3):340–52.
21. Knopman DS, Amieva H, Petersen RC, Chételat G, Holtzman DM, Hyman BT, et al. Alzheimer disease. *Nat Rev Dis Primer*. 2021 May 13;7(1):33.
22. Uddin S. Alzheimers Disease and You: Can Alzheimers Abduct Consciousness? *J Neurol Disord* [Internet]. 2017 [cited 2025 Oct 21];05(05). Available from: <https://www.omicsonline.org/open-access/alzheimers-disease-and-you-can-alzheimers-abduct-consciousness-2329-6895-1000e123-93546.html>
23. Hort J, Laczó J, Vyhnálek M, Bojar M, Bureš J, Vlček K. Spatial navigation deficit in amnesic mild cognitive impairment. *Proc Natl Acad Sci*. 2007 Mar 6;104(10):4042–7.
24. Cherrier MM, Mendez M, Perryman K. Route learning performance in Alzheimer disease patients. *Neuropsychiatry Neuropsychol Behav Neurol*. 2001;14(3):159–68.
25. Kessels RPC, Feijen J, Postma A. Implicit and explicit memory for spatial information in Alzheimer's disease. *Dement Geriatr Cogn Disord*. 2005;20(2–3):184–91.
26. Kim YJ, Park SW, Yeom HG, Bang MS, Kim JS, Chung CK, et al. A study on a robot arm driven by three-dimensional trajectories predicted from non-invasive neural signals. *Biomed Eng OnLine*. 2015 Aug 20;14(1):81.
27. Depannemaecker D. Would you publish unrealistic models? *Biol Cybern*. 2024 Dec 30;119(1):3.
28. Hodgkin AL, Huxley AF. A quantitative description of membrane current and its application to conduction and excitation in nerve. *J Physiol*. 1952 Aug 28;117(4):500–44.
29. Hines ML, Carnevale NT. The NEURON simulation environment. *Neural Comput*. 1997 Aug 15;9(6):1179–209.
30. GENESIS Reference Manual August 1, 1997: The Book of GENESIS [Internet]. [cited 2025 Oct 21]. Available from:

https://www.ncbs.res.in/images/stories/bhalla/old_server_backup/public_html/GENESIS/Hyperdoc/Manual-22.html

31. Rall W. Theoretical Significance of Dendritic Trees for Neuronal Input-Output Relations (1964). In: Segev I, Rinzel J, Shepherd GM, editors. The MIT Press; 1994 [cited 2025 Oct 21]. p. 122–46. Available from: <https://direct.mit.edu/books/book/2066/chapter/55783/Theoretical-Significance-of-Dendritic-Trees-for>
32. Destexhe A, Huguenard JR. Nonlinear Thermodynamic Models of Voltage-Dependent Currents. *J Comput Neurosci*. 2000 Nov 1;9(3):259–70.
33. Abbott LF. Lapicque's introduction of the integrate-and-fire model neuron (1907). *Brain Res Bull*. 1999 Nov 1;50(5):303–4.
34. Lapicque L. Recherches quantitatives sur l'excitation électrique des nerfs. *J Physiol Pathol Générale*. 1907;9:620–35.
35. Izhikevich EM. Simple model of spiking neurons. *IEEE Trans Neural Netw*. 2003 Nov;14(6):1569–72.
36. Spiegler A, Jirsa V. Systematic approximations of neural fields through networks of neural masses in the virtual brain. *NeuroImage*. 2013 Dec;83:704–25.
37. Jansen BH, Rit VG. Electroencephalogram and visual evoked potential generation in a mathematical model of coupled cortical columns. *Biol Cybern*. 1995 Sep;73(4):357–66.
38. Jansen BH, Zouridakis G, Brandt ME. A neurophysiologically-based mathematical model of flash visual evoked potentials. *Biol Cybern*. 1993;68(3):275–83.
39. Wendling F, Bellanger JJ, Bartolomei F, Chauvel P. Relevance of nonlinear lumped-parameter models in the analysis of depth-EEG epileptic signals. *Biol Cybern*. 2000 Sep 1;83(4):367–78.
40. Wendling F, Bartolomei F, Bellanger JJ, Chauvel P. Epileptic fast activity can be explained by a model of impaired GABAergic dendritic inhibition. *Eur J Neurosci*. 2002 May;15(9):1499–508.
41. Wendling F, Hernandez A, Bellanger JJ, Chauvel P, Bartolomei F. Interictal to ictal transition in human temporal lobe epilepsy: insights from a computational model of intracerebral EEG. *J Clin Neurophysiol Off Publ Am Electroencephalogr Soc*. 2005 Oct;22(5):343–56.
42. Ritter P, Schirner M, McIntosh AR, Jirsa VK. The virtual brain integrates computational modeling and multimodal neuroimaging. *Brain Connect*. 2013;3(2):121–45.
43. Schirner M, McIntosh AR, Jirsa V, Deco G, Ritter P. Inferring multi-scale neural mechanisms with brain network modelling. *eLife*. 2018 Jan 8;7:e28927.
44. Jirsa VK, Sporns O, Breakspear M, Deco G, McIntosh AR. Towards the virtual brain: network modeling of the intact and the damaged brain. *Arch Ital Biol*. 2010 Sep;148(3):189–205.

45. Sanz-Leon P, Knock SA, Spiegler A, Jirsa VK. Mathematical framework for large-scale brain network modeling in The Virtual Brain. *NeuroImage*. 2015 May 1;111:385–430.
46. Amunts K, Axer M, Bitsch L, Bjaalie J, Brovelli A, Caspers S, et al. The coming decade of digital brain research - A vision for neuroscience at the intersection of technology and computing [Internet]. Zenodo; 2022 Mar [cited 2025 Oct 21]. Available from: <https://zenodo.org/records/6345821>
47. Grieves MW. Virtually Intelligent Product Systems: Digital and Physical Twins. In: *Complex Systems Engineering: Theory and Practice* [Internet]. American Institute of Aeronautics and Astronautics, Inc.; 2019 [cited 2025 Oct 21]. p. 175–200. (Progress in Astronautics and Aeronautics; vol. Volume 256). Available from: <https://arc.aiaa.org/doi/10.2514/5.9781624105654.0175.0200>
48. Wang HE, Dollomaja B, Triebkorn P, Duma GM, Williamson A, Makhalova J, et al. Virtual brain twins for stimulation in epilepsy. *Nat Comput Sci*. 2025 Sep;5(9):754–68.
49. D’Angelo E, Jirsa V. The quest for multiscale brain modeling. *Trends Neurosci*. 2022 Oct 1;45(10):777–90.
50. Anderson DR. *Model Based Inference in the Life Sciences: A Primer on Evidence* [Internet]. New York, NY: Springer; 2008 [cited 2025 Oct 24]. Available from: <http://link.springer.com/10.1007/978-0-387-74075-1>
51. Hashemi M, Vattikonda AN, Sip V, Guye M, Bartolomei F, Woodman MM, et al. The Bayesian Virtual Epileptic Patient: A probabilistic framework designed to infer the spatial map of epileptogenicity in a personalized large-scale brain model of epilepsy spread. 2020 [cited 2024 Apr 2]; Available from: <https://doi.org/10.1016/j.neuroimage.2020.116839>
52. Wang HE, Woodman M, Triebkorn P, Lemarechal JD, Jha J, Dollomaja B, et al. Delineating epileptogenic networks using brain imaging data and personalized modeling in drug-resistant epilepsy. *Sci Transl Med* [Internet]. 2023 Jan 25 [cited 2024 Apr 2];15(680). Available from: <https://pubmed.ncbi.nlm.nih.gov/36696482/>
53. Jirsa V, Wang H, Triebkorn P, Hashemi M, Jha J, Gonzalez-Martinez J, et al. Personalised virtual brain models in epilepsy. *Lancet Neurol*. 2023 May;22(5):443–54.
54. Triebkorn P, Stefanovski L, Dhindsa K, Diaz-Cortes MA, Bey P, Bülau K, et al. Brain simulation augments machine-learning-based classification of dementia. *Alzheimers Dement N Y N*. 2022;8(1):e12303.
55. Yalçinkaya BH, Ziaemehr A, Fousek J, Hashemi M, Lavanga M, Solodkin A, et al. Personalized virtual brains of Alzheimer’s Disease link dynamical biomarkers of fMRI with increased local excitability [Internet]. *medRxiv*; 2023 [cited 2025 Apr 10]. p. 2023.01.11.23284438. Available from: <https://www.medrxiv.org/content/10.1101/2023.01.11.23284438v1>
56. Andrieu C, de Freitas N, Doucet A, Jordan MI. An Introduction to MCMC for Machine Learning. *Mach Learn*. 2003 Jan 1;50(1):5–43.

57. Cranmer K, Brehmer J, Louppe G. The frontier of simulation-based inference. *Proc Natl Acad Sci U S A*. 2020 Dec 1;117(48):30055–62.
58. Boelts J, Lueckmann JM, Gao R, Macke JH. Flexible and efficient simulation-based inference for models of decision-making. Wyart V, Behrens TE, Acerbi L, Daunizeau J, editors. *eLife*. 2022 Jul 27;11:e77220.
59. Hashemi M, Vattikonda AN, Jha J, Sip V, Woodman MM, Bartolomei F, et al. Amortized Bayesian inference on generative dynamical network models of epilepsy using deep neural density estimators. *Neural Netw Off J Int Neural Netw Soc*. 2023 Jun 1;163:178–94.
60. Corkin S. What's new with the amnesic patient H.M.? *Nat Rev Neurosci*. 2002 Feb;3(2):153–60.
61. US Elsevier Health [Internet]. [cited 2025 Oct 24]. Netter Atlas of Human Anatomy: Classic Regional - 9780323680424. Available from: <https://www.us.elsevierhealth.com/netter-atlas-of-human-anatomy-classic-regional-approach-9780323680424.html>
62. O'Carroll CM, Martin SJ, Sandin J, Frenguelli B, Morris RGM. Dopaminergic modulation of the persistence of one-trial hippocampus-dependent memory. *Learn Mem*. 2006;13(6):760–9.
63. Kandel ER, Schwartz JH, Jessell TM, Siegelbaum S, Hudspeth AJ. *Principles of Neural Science*. 6th, McGraw-Hill Education ed. 2021.
64. Bhattacharyya KB. James Wenceslaus Papez, His Circuit, and Emotion. *Ann Indian Acad Neurol*. 2017;20(3):207–10.
65. Tolman EC, Ritchie BF, Kalish D. Studies in spatial learning. I. Orientation and the short-cut. *J Exp Psychol Gen*. 1992;121(4):429–34.
66. O'Keefe J, Dostrovsky J. The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. *Brain Res*. 1971 Nov 12;34(1):171–5.
67. Muller RU, Ranck JB, Taube JS. Head direction cells: properties and functional significance. *Curr Opin Neurobiol*. 1996 Apr 1;6(2):196–206.
68. Taube JS, Muller RU, Ranck JB. Head-direction cells recorded from the postsubiculum in freely moving rats. I. Description and quantitative analysis. *J Neurosci Off J Soc Neurosci*. 1990;10(2):420–35.
69. Sargolini F, Fyhn M, Hafting T, McNaughton BL, Witter MP, Moser MB, et al. Conjunctive representation of position, direction, and velocity in entorhinal cortex. *Science*. 2006 May 5;312(5774):758–62.
70. Lever C, Burton S, Jeewajee A, O'Keefe J, Burgess N. Boundary vector cells in the subiculum of the hippocampal formation. *J Neurosci Off J Soc Neurosci*. 2009 Aug 5;29(31):9771–7.

71. Solstad T, Boccara CN, Kropff E, Moser MB, Moser EI. Representation of geometric borders in the entorhinal cortex. *Science*. 2008 Dec 19;322(5909):1865–8.
72. Hafting T, Fyhn M, Molden S, Moser MB, Moser EI. Microstructure of a spatial map in the entorhinal cortex. *Nature*. 2005 Aug 11;436(7052):801–6.
73. Kropff E, Carmichael JE, Moser MB, Moser EI. Speed cells in the medial entorhinal cortex. *Nature*. 2015 Jul 23;523(7561):419–24.
74. Wilson MA, McNaughton BL. Dynamics of the hippocampal ensemble code for space. *Science*. 1993;261(5124):1055–8.
75. Fried I, MacDonald KA, Wilson CL. Single neuron activity in human hippocampus and amygdala during recognition of faces and objects. *Neuron*. 1997;18(5):753–65.
76. Ulanovsky N, Moss CF. Hippocampal cellular and network activity in freely moving echolocating bats. *Nat Neurosci*. 2007 Feb;10(2):224–33.
77. Hazama Y, Tamura R. Data on the activity of place cells in the hippocampal CA1 subfield of a monkey performing a shuttling task. *Data Brief [Internet]*. 2019 Oct 1 [cited 2022 Mar 14];26. Available from: <https://pubmed.ncbi.nlm.nih.gov/31538104/>
78. Hazama Y, Tamura R. Effects of self-locomotion on the activity of place cells in the hippocampus of a freely behaving monkey. *Neurosci Lett*. 2019 May 14;701:32–7.
79. Ekstrom AD, Kahana MJ, Caplan JB, Fields TA, Isham EA, Newman EL, et al. Cellular networks underlying human spatial navigation. *Nature*. 2003 Sep 11;425(6954):184–7.
80. Bittner KC, Grienberger C, Vaidya SP, Milstein AD, Macklin JJ, Suh J, et al. Conjunctive input processing drives feature selectivity in hippocampal CA1 neurons. *Nat Neurosci*. 2015 Aug 30;18(8):1133–42.
81. Migliore M, Novara G, Tegolo D. Single neuron binding properties and the magical number 7. *Hippocampus*. 2008 Nov;18(11):1122–30.
82. Quiroga RQ, Reddy L, Kreiman G, Koch C, Fried I. Invariant visual representation by single neurons in the human brain. *Nature*. 2005 Jun 23;435(7045):1102–7.
83. Kornblith S, Quiroga R, Koch C, Fried I, Mormann F. Persistent Single-Neuron Activity during Working Memory in the Human Medial Temporal Lobe. *Curr Biol CB*. 2017 Apr 3;27(7):1026–32.
84. Romani A, Schürmann F, Markram H, Migliore M. Reconstruction of the Hippocampus. *Adv Exp Med Biol*. 2022;1359:261–83.
85. Gandolfi D, Mapelli J, Solinas SMG, et al. Full-scale scaffold model of the human hippocampus CA1 area. *Nat Comput Sci*. 2023;3:264–76.
86. Kastellakis G, Silva AJ, Poirazi P. Linking Memories across Time via Neuronal and Dendritic Overlaps in Model Neurons with Active Dendrites. *Cell Rep*. 2016 Nov 1;17(6):1491–504.

87. Lisman J. Working memory: the importance of theta and gamma oscillations. *Curr Biol CB* [Internet]. 2010 Jun 8 [cited 2022 Mar 14];20(11). Available from: <https://pubmed.ncbi.nlm.nih.gov/20541499/>
88. Jensen O, Kaiser J, Lachaux JP. Human gamma-frequency oscillations associated with attention and memory. *Trends Neurosci*. 2007 Jul;30(7):317–24.
89. Gray CM. Synchronous oscillations in neuronal systems: mechanisms and functions. *J Comput Neurosci*. 1994 Jun;1(1–2):11–38.
90. Bianchi D, Michele PD, Marchetti C, Tirozzi B, Cuomo S, Marie H, et al. Effects of increasing CREB-dependent transcription on the storage and recall processes in a hippocampal CA1 microcircuit. *Hippocampus*. 2014 Feb;24(2):165–77.
91. Nishiyama M, Hong K, Mikoshiba K, Poo MM, Kato K. Calcium stores regulate the polarity and input specificity of synaptic modification. *Nature*. 2000 Nov 30;408(6812):584–8.
92. Hansen N, Manahan-Vaughan D. Locus Coeruleus Stimulation Facilitates Long-Term Depression in the Dentate Gyrus That Requires Activation of β -Adrenergic Receptors. *Cereb Cortex N Y N* 1991. 2015 Jul 1;25(7):1889–96.
93. Bittner KC, Milstein AD, Grienberger C, Romani S, Magee JC. Behavioral time scale synaptic plasticity underlies CA1 place fields. *Science*. 2017 Sep 8;357:1033–6.
94. O’Keefe J. The Hippocampus as a Cognitive Map. 1978.
95. Knierim JJ, Rao G. Distal landmarks and hippocampal place cells: effects of relative translation versus rotation. *Hippocampus*. 2003;13(5):604–17.
96. Knierim JJ, Kudrimoti HS, McNaughton BL. Place cells, head direction cells, and the learning of landmark stability. *J Neurosci Off J Soc Neurosci*. 1995;15(3 Pt 1):1648–59.
97. Yoder RM, Clark BJ, Taube JS. Origins of landmark encoding in the brain. *Trends Neurosci*. 2011;34(11):561–71.
98. Alme CB, Miao C, Jezek K, Treves A, Moser EI, Moser MB. Place cells in the hippocampus: eleven maps for eleven rooms. *Proc Natl Acad Sci U S A*. 2014 Dec 30;111(52):18428–35.
99. Hok V, Chah E, Reilly RB, O’Mara SM. Hippocampal dynamics predict interindividual cognitive differences in rats. *J Neurosci Off J Soc Neurosci*. 2012 Mar 7;32(10):3540–51.
100. Mielke MM. Sex and Gender Differences in Alzheimer’s Disease Dementia. *Psychiatr Times*. 2018 Dec 30;35(11):14.
101. Uddin MS, Ashraf GM, Uddin MS, Ashraf GM. Introductory Chapter: Alzheimer’s Disease—The Most Common Cause of Dementia. In: *Advances in Dementia Research* [Internet]. IntechOpen; 2018 [cited 2024 Nov 5]. Available from: <https://www.intechopen.com/chapters/64605>

102. Giebel CM, Sutcliffe C, Stolt M, Karlsson S, Renom-Guiteras A, Soto M, et al. Deterioration of basic activities of daily living and their impact on quality of life across different cognitive stages of dementia: a European study. *Int Psychogeriatr*. 2014 Aug 1;26(8):1283–93.
103. Maresova P, Hruska J, Klimova B, Barakovic S, Krejcar O.

Activities of Daily Living and Associated Costs in the Most Widespread Neurodegenerative Diseases: A Systematic Review

. *Clin Interv Aging*. 2020 Oct 2;15:1841–62.
104. Tekin S, Fairbanks LA, O'Connor S, Rosenberg S, Cummings JL. Activities of Daily Living in Alzheimer's Disease: Neuropsychiatric, Cognitive, and Medical Illness Influences. *Am J Geriatr Psychiatry*. 2001 Dec 1;9(1):81–6.
105. Buckley RF, Saling MM, Frommann I, Wolfsgrubner S, Wagner M. Subjective Cognitive Decline from a Phenomenological Perspective: A Review of the Qualitative Literature. *J Alzheimers Dis JAD*. 2015 Sep 24;48 Suppl 1:S125-140.
106. Jahn H. Memory loss in Alzheimer's disease. *Dialogues Clin Neurosci*. 2013 Dec;15(4):445–54.
107. Morganti F, Stefanini S, Riva G. From allo- to egocentric spatial ability in early Alzheimer's disease: a study with virtual reality spatial tasks. *Cogn Neurosci*. 2013;4(3–4):171–80.
108. Verma M, Howard RJ. Semantic memory and language dysfunction in early Alzheimer's disease: a review. *Int J Geriatr Psychiatry*. 2012 Dec;27(12):1209–17.
109. Allain P, Etcharry-Bouyx F, Verny C. Executive functions in clinical and preclinical Alzheimer's disease. *Rev Neurol (Paris)*. 2013 Oct 1;169(10):695–708.
110. Belleville S. S3-02-05: Working memory and control of attention in persons with Alzheimer's disease and mild cognitive impairment. *Alzheimers Dement*. 2010;6(4S_Part_4):S122–S122.
111. Monacelli AM, Cushman LA, Kavcic V, Duffy CJ. Spatial disorientation in Alzheimer's disease. *Neurology*. 2003 Dec 9;61(11):1491–7.
112. Peters-Founshtein G, Gazit L, Naveh T, Domachevsky L, Korczyn AD, Bernstine H, et al. Lost in space(s): Multimodal neuroimaging of disorientation along the Alzheimer's disease continuum. *Hum Brain Mapp*. 2024;45(4):e26623.
113. Botto R, Callai N, Cermelli A, Causarano L, Rainero I. Anxiety and depression in Alzheimer's disease: a systematic review of pathogenetic mechanisms and relation to cognitive decline. *Neurol Sci*. 2022;43(7):4107–24.
114. Cummings JL, Raman R, Ernstom K, Salmon D, Ferris SH, Group for the ADCS. ADCS Prevention Instrument Project: Behavioral Measures in Primary Prevention Trials. *Alzheimer Dis Assoc Disord*. 2006 Dec;20:S147.
115. Mega MS, Cummings JL, Fiorello T, Gornbein J. The spectrum of behavioral changes in Alzheimer's disease. *Neurology*. 1996 Jan;46(1):130–5.

116. Zhao QF, Tan L, Wang HF, Jiang T, Tan MS, Tan L, et al. The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis. *J Affect Disord*. 2016 Jan 15;190:264–71.
117. Romano A, Troisi Lopez E, Cipriano L, Liparoti M, Minino R, Polverino A, et al. Topological changes of fast large-scale brain dynamics in mild cognitive impairment predict early memory impairment: a resting-state, source reconstructed, magnetoencephalography study. *Neurobiol Aging*. 2023 Dec 1;132:36–46.
118. Jack Jr. CR, Andrews JS, Beach TG, Buracchio T, Dunn B, Graf A, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimers Dement*. 2024;20(8):5143–69.
119. Bierer LM, Hof PR, Purohit DP, Carlin L, Schmeidler J, Davis KL, et al. Neocortical Neurofibrillary Tangles Correlate With Dementia Severity in Alzheimer's Disease. *Arch Neurol*. 1995 Jan 1;52(1):81–8.
120. Fukutani Y, Cairns NJ, Shiozawa M, Sasaki K, Sudo S, Isaki K, et al. Neuronal loss and neurofibrillary degeneration in the hippocampal cortex in late-onset sporadic Alzheimer's disease. *Psychiatry Clin Neurosci*. 2000;54(5):523–9.
121. Delbeuck X, Collette F, Van der Linden M. Is Alzheimer's disease a disconnection syndrome?: Evidence from a crossmodal audio-visual illusory experiment. *Neuropsychologia*. 2007 Jan 1;45(14):3315–23.
122. Paitel ER, Otteman CBD, Polking MC, Licht HJ, Nielson KA. Functional and effective EEG connectivity patterns in Alzheimer's disease and mild cognitive impairment: a systematic review. *Front Aging Neurosci*. 2025;17:1496235.
123. Friston KJ. Functional and effective connectivity: a review. *Brain Connect*. 2011;1(1):13–36.
124. Stam CJ. Modern network science of neurological disorders. *Nat Rev Neurosci*. 2014 Oct;15(10):683–95.
125. Fornito A, Zalesky A, Breakspear M. The connectomics of brain disorders. *Nat Rev Neurosci*. 2015 Mar;16(3):159–72.
126. Hutchison RM, Womelsdorf T, Gati JS, Everling S, Menon RS. Resting-state networks show dynamic functional connectivity in awake humans and anesthetized macaques: Dynamic Functional Connectivity. *Hum Brain Mapp*. 2013 Sep;34(9):2154–77.
127. Zalesky A, Fornito A, Cocchi L, Gollo LL, Breakspear M. Time-resolved resting-state brain networks. *Proc Natl Acad Sci*. 2014 Jul 15;111(28):10341–6.
128. Cipriano L, Minino R, Liparoti M, Polverino A, Romano A, Bonavita S, et al. Flexibility of brain dynamics is increased and predicts clinical impairment in relapsing-remitting but not in secondary progressive multiple sclerosis. *Brain Commun*. 2024;6(2):fcae112.

129. Polverino A, Troisi Lopez E, Minino R, Liparoti M, Romano A, Trojsi F, et al. Flexibility of Fast Brain Dynamics and Disease Severity in Amyotrophic Lateral Sclerosis. *Neurology*. 2022 Nov 22;99(21):e2395–405.
130. Sorrentino P, Rucco R, Baseliace F, De Micco R, Tessitore A, Hillebrand A, et al. Flexible brain dynamics underpins complex behaviours as observed in Parkinson's disease. *Sci Rep [Internet]*. 2021 Dec 1 [cited 2024 Mar 14];11(1). Available from: [/pmc/articles/PMC7892831/](https://pubmed.ncbi.nlm.nih.gov/34111111/)
131. Preti MG, Bolton TA, Van De Ville D. The dynamic functional connectome: State-of-the-art and perspectives. *NeuroImage*. 2017 Oct 15;160:41–54.
132. Hansen ECA, Battaglia D, Spiegler A, Deco G, Jirsa VK. Functional connectivity dynamics: Modeling the switching behavior of the resting state. *NeuroImage*. 2015 Jan 15;105:525–35.
133. Battaglia D, Boudou T, Hansen ECA, Lombardo D, Chettouf S, Daffertshofer A, et al. Dynamic Functional Connectivity between order and randomness and its evolution across the human adult lifespan. *NeuroImage*. 2020 Nov 15;222:117156.
134. Breyton M, Fousek J, Rabuffo G, Sorrentino P, Kusch L, Massimini M, et al. Spatiotemporal brain complexity quantifies consciousness outside of perturbation paradigms. *eLife [Internet]*. 2024 Aug 26 [cited 2025 Mar 18];13. Available from: <https://elifesciences.org/reviewed-preprints/98920>
135. Jafari Z, Kolb BE, Mohajerani MH. Neural oscillations and brain stimulation in Alzheimer's disease. *Prog Neurobiol*. 2020 Nov;194:101878.
136. Jeong J. EEG dynamics in patients with Alzheimer's disease. *Clin Neurophysiol Off J Int Fed Clin Neurophysiol*. 2004 Jul;115(7):1490–505.
137. van den Heuvel MP, Hulshoff Pol HE. Exploring the brain network: a review on resting-state fMRI functional connectivity. *Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol*. 2010 Aug;20(8):519–34.
138. Lachaux J, Rodriguez E, Martinerie J, Varela FJ. Measuring phase synchrony in brain signals. *Hum Brain Mapp*. 1999 Nov 30;8(4):194–208.
139. Sadaghiani S, Dombert PL, Løvstad M, Funderud I, Meling TR, Endestad T, et al. Lesions to the Fronto-Parietal Network Impact Alpha-Band Phase Synchrony and Cognitive Control. *Cereb Cortex N Y N 1991*. 2019 Sep 13;29(10):4143–53.
140. Gaby A. Multiple Sclerosis. *Glob Adv Health Med*. 2013;2(1):50–6.
141. Ghasemi N, Razavi S, Nikzad E. Multiple Sclerosis: Pathogenesis, Symptoms, Diagnoses and Cell-Based Therapy Citation: Ghasemi N, Razavi Sh, Nikzad E. Multiple sclerosis: pathogenesis, symptoms, diagnoses and cell-based therapy. *Cell J*. 2017;19(191).
142. Bernard CCA, de Rosbo NK. Multiple sclerosis: an autoimmune disease of multifactorial etiology. *Curr Opin Immunol*. 1992;4(6).

143. Filippi M, Bar-Or A, Piehl F, Preziosa P, Solari A, Vukusic S, et al. Multiple sclerosis. *Nat Rev Dis Primer* [Internet]. 2018 Dec 1 [cited 2024 Jan 30];4(1). Available from: <https://pubmed.ncbi.nlm.nih.gov/30410033/>
144. Yamout BI, Alroughani R. Multiple Sclerosis. *Semin Neurol*. 2018 Apr 1;38(2):212–25.
145. Fowler CJ, Gilliatt RW. Conduction velocity and conduction block after experimental ischaemic nerve injury. *J Neurol Sci*. 1981;52(2–3):221–38.
146. Gutiérrez R, Boison D, Heinemann U, Stoffel W. Decompaction of CNS myelin leads to a reduction of the conduction velocity of action potentials in optic nerve. *Neurosci Lett*. 1995;195(2).
147. Reutskiy S, Rossoni E, Tirozzi B. Conduction in bundles of demyelinated nerve fibers: Computer simulation. *Biol Cybern*. 2003;89(6).
148. Gillespie MJ, Stein RB. The relationship between axon diameter, myelin thickness and conduction velocity during atrophy of mammalian peripheral nerves. *Brain Res*. 1983;259(1).
149. Ritchie JM. On the relation between fibre diameter and conduction velocity in myelinated nerve fibres. *Proc R Soc Lond - Biol Sci*. 1982;217(1206).
150. Sanders FK, Whitteridge D. Conduction velocity and myelin thickness in regenerating nerve fibres. *J Physiol*. 1946 Sep 18;105(2):152–74.
151. Leocani L, Medaglini S, Comi G. Evoked potentials in monitoring multiple sclerosis. *Neurol Sci*. 2000;21(8):S889–91.
152. Drakesmith M, Jones DK. Mapping axon conduction delays in vivo from microstructural MRI. *bioRxiv*. 2019 Feb 8;503763.
153. Mancini M, Tian Q, Fan Q, Cercignani M, Huang SY. Dissecting whole-brain conduction delays through MRI microstructural measures. *Brain Struct Funct*. 2021;226:2651–63.
154. Ashburner J, Friston K. Multimodal image coregistration and partitioning--a unified framework. *NeuroImage*. 1997;6(3):209–17.
155. Cabral J, Castaldo F, Vohryzek J, Litvak V, Bick C, Lambiotte R, et al. Metastable oscillatory modes emerge from synchronization in the brain spacetime connectome. *Commun Phys* [Internet]. 2022 Dec 1 [cited 2024 Mar 18];5(1). Available from: <https://pubmed.ncbi.nlm.nih.gov/38288392/>
156. Sorrentino P, Pathak A, Ziaemehr A, Lopez ET, Cipriano L, Romano A, et al. The virtual multiple sclerosis patient: on the clinical-radiological paradox. *medRxiv*. 2023 Dec 1;2023.12.01.23299274.
157. Cajochen C, Brunner DP, Kräuchi K, Graw P, Wirz-Justice A. Power density in theta/alpha frequencies of the waking EEG progressively increases during sustained wakefulness. *Sleep*. 1995 Dec;18(10):890–4.

158. Cantero JL, Atienza M, Salas RM. Human alpha oscillations in wakefulness, drowsiness period, and REM sleep: different electroencephalographic phenomena within the alpha band. *Neurophysiol Clin Clin Neurophysiol*. 2002 Jan;32(1):54–71.
159. Sutherland RJ, Whishaw IQ, Kolb B. A behavioural analysis of spatial localization following electrolytic, kainate- or colchicine-induced damage to the hippocampal formation in the rat. *Behav Brain Res*. 1983;7(2):133–53.
160. Yang C, Mammen L, Kim B, Li M, Robson DN, Li JM. A population code for spatial representation in the zebrafish telencephalon. *Nature*. 2024 Oct;634(8033):397–406.
161. Vlček K, Laczó J. Neural Correlates of Spatial Navigation Changes in Mild Cognitive Impairment and Alzheimer's Disease. *Front Behav Neurosci* [Internet]. 2014 Mar 17 [cited 2025 Oct 30];8. Available from: <https://www.frontiersin.org/journals/behavioral-neuroscience/articles/10.3389/fnbeh.2014.00089/full>
162. Kalová E, Vlček K, Jarolímová E, Bureš J. Allothetic orientation and sequential ordering of places is impaired in early stages of Alzheimer's disease: corresponding results in real space tests and computer tests. *Behav Brain Res*. 2005 Apr 30;159(2):175–86.
163. Berkowitz LE, Harvey RE, Clark BJ. Chapter 43 - Spatial navigation and Alzheimer's disease. In: Martin CR, Preedy VR, editors. *Genetics, Neurology, Behavior, and Diet in Dementia* [Internet]. Academic Press; 2020 [cited 2025 Oct 30]. p. 677–92. Available from: <https://www.sciencedirect.com/science/article/pii/B9780128158685000438>
164. Tsetsenis T, Badyna JK, Wilson JA, Zhang X, Krizman EN, Subramaniyan M, et al. Midbrain dopaminergic innervation of the hippocampus is sufficient to modulate formation of aversive memories. *Proc Natl Acad Sci*. 2021 Oct 5;118(40):e2111069118.
165. Gasbarri A, Verney C, Innocenzi R, Campana E, Pacitti C. Mesolimbic dopaminergic neurons innervating the hippocampal formation in the rat: a combined retrograde tracing and immunohistochemical study. *Brain Res*. 1994 Dec 30;668(1–2):71–9.
166. Gasbarri A, Sulli A, Packard MG. The dopaminergic mesencephalic projections to the hippocampal formation in the rat. *Prog Neuropsychopharmacol Biol Psychiatry*. 1997 Jan;21(1):1–22.
167. Gasbarri A, Packard MG, Campana E, Pacitti C. Anterograde and retrograde tracing of projections from the ventral tegmental area to the hippocampal formation in the rat. *Brain Res Bull*. 1994;33(4):445–52.
168. Zipser D. Biologically plausible models of place recognition and goal location. *Parallel Distrib Process Explor Microstruct Cogn*. 1986;432–70.
169. Sharp PE. Computer simulation of hippocampal place cells. *Psychobiol*. 1991;19(2):103–15.
170. Hartley T, Burgess N, Lever C, Cacucci F, O'Keefe J. Modeling place fields in terms of the cortical inputs to the hippocampus. *Hippocampus*. 2000;10(4):369–79.

171. Barry C, Burgess N. Learning in a geometric model of place cell firing. *Hippocampus*. 2007;17(9):786–800.
172. Watanabe H, Bagarinao E, Yokoi T, Yamaguchi H, Ishigaki S, Mausuda M, et al. Tau Accumulation and Network Breakdown in Alzheimer's Disease. *Adv Exp Med Biol*. 2019;1184:231–40.
173. Yu M, Sporns O, Saykin AJ. The human connectome in Alzheimer disease - relationship to biomarkers and genetics. *Nat Rev Neurol*. 2021 Sep;17(9):545–63.
174. Hampel H, Hardy J, Blennow K, Chen C, Perry G, Kim SH, et al. The Amyloid- β Pathway in Alzheimer's Disease. *Mol Psychiatry*. 2021 Oct;26(10):5481–503.
175. Zhang Y, Chen H, Li R, Sterling K, Song W. Amyloid β -based therapy for Alzheimer's disease: challenges, successes and future. *Signal Transduct Target Ther*. 2023 Jun 30;8(1):1–26.
176. Dubois B, Hampel H, Feldman HH, Scheltens P, Aisen P, Andrieu S, et al. Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. *Alzheimers Dement J Alzheimers Assoc*. 2016 Mar;12(3):292–323.
177. Jansen WJ, Ossenkoppele R, Knol DL, Tijms BM, Scheltens P, Verhey FRJ, et al. Prevalence of Cerebral Amyloid Pathology in Persons Without Dementia: A Meta-analysis. *JAMA*. 2015 May 19;313(19):1924–38.
178. Kurkinen M, Fułek M, Fułek K, Beszlej JA, Kurpas D, Leszek J. The Amyloid Cascade Hypothesis in Alzheimer's Disease: Should We Change Our Thinking? *Biomolecules*. 2023 Mar 1;13(3):453.
179. Gallego-Rudolf J, Wiesman AI, Pichet Binette A, Villeneuve S, Baillet S. Synergistic association of A β and tau pathology with cortical neurophysiology and cognitive decline in asymptomatic older adults. *Nat Neurosci*. 2024 Nov;27(11):2130–7.
180. Bastos AM, Schoffelen JM. A Tutorial Review of Functional Connectivity Analysis Methods and Their Interpretational Pitfalls. *Front Syst Neurosci*. 2015;9:175.
181. Cao J, Zhao Y, Shan X, Wei H liang, Guo Y, Chen L, et al. Brain functional and effective connectivity based on electroencephalography recordings: A review. *Hum Brain Mapp*. 2022;43(2):860–79.
182. Cohen MX. Analyzing Neural Time Series Data: Theory and Practice [Internet]. The MIT Press; 2014 [cited 2025 Jul 2]. Available from: <https://direct.mit.edu/books/monograph/4013/Analyzing-Neural-Time-Series-DataTheory-and>
183. Rueda AD, Lau KM, Saito N, Harvey D, Risacher SL, Aisen PS, et al. Self-rated and informant-rated everyday function in comparison to objective markers of Alzheimer's disease. *Alzheimers Dement*. 2015;11(9):1080–9.
184. Cover KS, Vrenken H, Geurts JJG, Van Oosten BW, Jelles B, Polman CH, et al. Multiple sclerosis patients show a highly significant decrease in alpha band

- interhemispheric synchronization measured using MEG. *NeuroImage*. 2006 Feb 1;29(3):783–8.
185. Bsar-Eroglu C, Warecka K, Schürmann M, Başar E. Visual evoked potentials in multiple sclerosis: Frequency response shows reduced alpha amplitude. *Int J Neurosci*. 1993;73(3–4):235–58.
 186. Van Schependom J, Vidaurre D, Costers L, Sjøgård M, Sima DM, Smeets D, et al. Increased brain atrophy and lesion load is associated with stronger lower alpha MEG power in multiple sclerosis patients. *NeuroImage Clin* [Internet]. 2021 Jan 1 [cited 2024 Mar 19];30. Available from: [/pmc/articles/PMC8022249/](https://pubmed.ncbi.nlm.nih.gov/32745679/)
 187. Berman S, Backner Y, Krupnik R, Paul F, Petrou P, Karussis D, et al. Conduction delays in the visual pathways of progressive multiple sclerosis patients covary with brain structure. *NeuroImage* [Internet]. 2020 Nov 1 [cited 2024 Mar 19];221. Available from: <https://pubmed.ncbi.nlm.nih.gov/32745679/>
 188. Gollo LL, Roberts JA, Cropley VL, Di Biase MA, Pantelis C, Zalesky A, et al. Fragility and volatility of structural hubs in the human connectome. *Nat Neurosci*. 2018 Aug;21(8):1107–16.
 189. Abela E, Pawley AD, Tangwiriyasakul C, Yaakub SN, Chowdhury FA, Elwes RDC, et al. Slower alpha rhythm associates with poorer seizure control in epilepsy. *Ann Clin Transl Neurol*. 2019 Feb;6(2):333–43.
 190. Corlier J, Carpenter LL, Wilson AC, Tirrell E, Gobin AP, Kavanaugh B, et al. The relationship between individual alpha peak frequency and clinical outcome with repetitive Transcranial Magnetic Stimulation (rTMS) treatment of Major Depressive Disorder (MDD). *Brain Stimulat*. 2019;12(6):1572–8.
 191. Garcés P, Vicente R, Wibrál M, Pineda-Pardo JÁ, López ME, Aurtenetxe S, et al. Brain-wide slowing of spontaneous alpha rhythms in mild cognitive impairment. *Front Aging Neurosci*. 2013 Dec 27;5:100.
 192. Ippolito G, Bertaccini R, Tarasi L, Di Gregorio F, Trajkovic J, Battaglia S, et al. The Role of Alpha Oscillations among the Main Neuropsychiatric Disorders in the Adult and Developing Human Brain: Evidence from the Last 10 Years of Research. *Biomedicines*. 2022 Dec 8;10(12):3189.