Cross-Frequency Coupling for Prediction Error Evaluation: A laNMM Modeling Approach

Giulio Ruffini, Edmundo Lopez-Sola, Raul Palma, Roser Sanchez-Todo, Jakub Vohryzek, Francesca Castaldo, and Karl Friston

Neuroelectrics Barcelona, Barcelona
Universitat Pompeu Fabra (UPF), University College London
(BARCCSYN 2025, May 23, 2025)

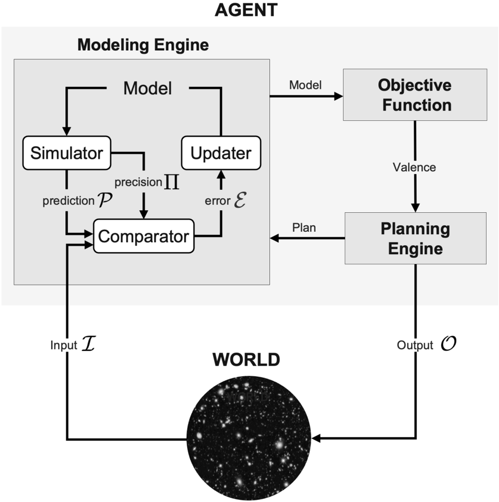
giulio.ruffini@neuroelectrics.com

neuroelectrics®

Introduction: Predictive Coding & LaNMM

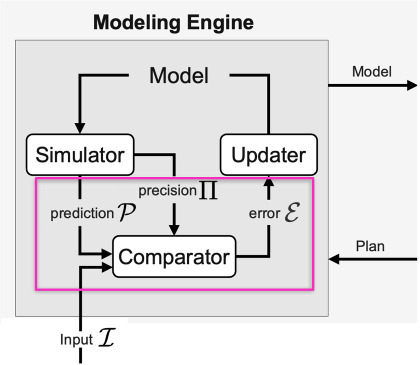
The algorithmic agent[2]

- A model for natural and artificial agenthood inspired in Algorithmic Information Theory[1;2].
- Minimal set of elements needed for an interacting homeostatic algorithmic system.
- To be connected with (neuro)biology!



The algorithmic agent[2]

- Here we focus on The **Comparator**: which compares data with predictions[1].
- How? Through oscillatory computation! Ok, but
- Where is the information in the brain?
- How is it “compared”?



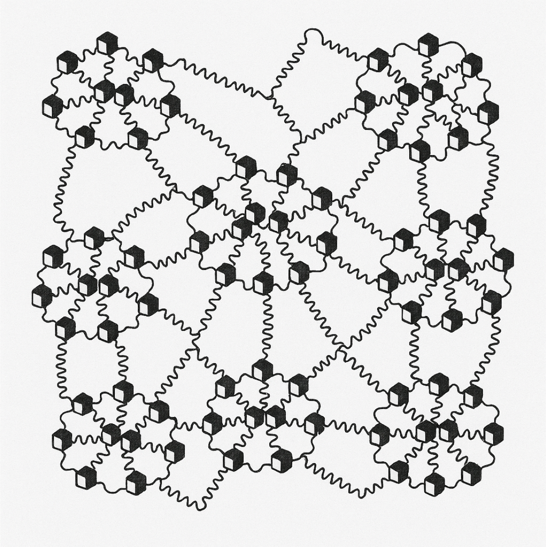
Motivation

- Neural implementation of predictive coding's comparator is unresolved: **how are mismatches (prediction errors) computed in cortical circuits?**
- A **Comparator** must subtract predictions (P) from inputs (I) and weight the difference by *precision* (confidence) for belief updating.
- **Open question:** How do neural networks perform this subtraction ($I - P$) and dynamic gain control (precision weighting) in real time?
- **Hypothesis:** Oscillatory cross-frequency coupling provides the mechanism. By leveraging interactions of slow and fast brain waves, the cortex could evaluate prediction errors and encode their precision.

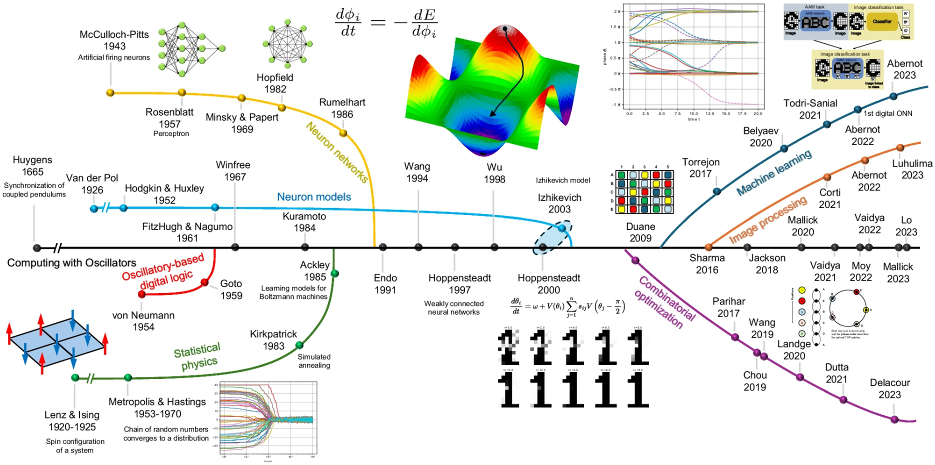
Predictive Coding Framework

- Brain as a modeling, **predictive agent**: continuously generating "top-down" predictions and comparing them with "bottom-up sensory" input (hierarchically, prediction errors).
- **Prediction errors propagate forward** to update higher-level beliefs; predictions **feed back** to explain away expected input.
- Neural oscillations play distinct roles: **fast** gamma ($\sim$30–100 Hz) activity conveys feedforward surprise (prediction errors), while **slower** alpha/beta (8–30 Hz) rhythms carry feedback predictions.
- **Cross-frequency coupling (CFC)** links these scales: slower oscillations modulate fast oscillation amplitude, coordinating hierarchical inference (precision-weighted error signaling). But, precisely, **how**?

How does this compute (Oscillatory Neural Networks)?

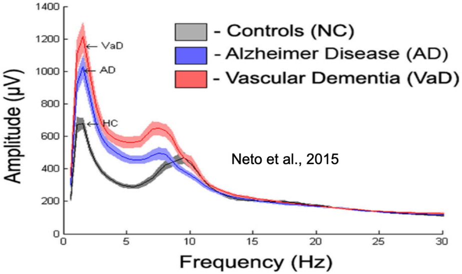


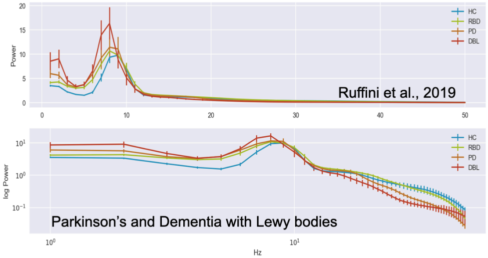
ONN Context (Todri-Sanial et al., 2024[3])



Implementation: the LaNMM model

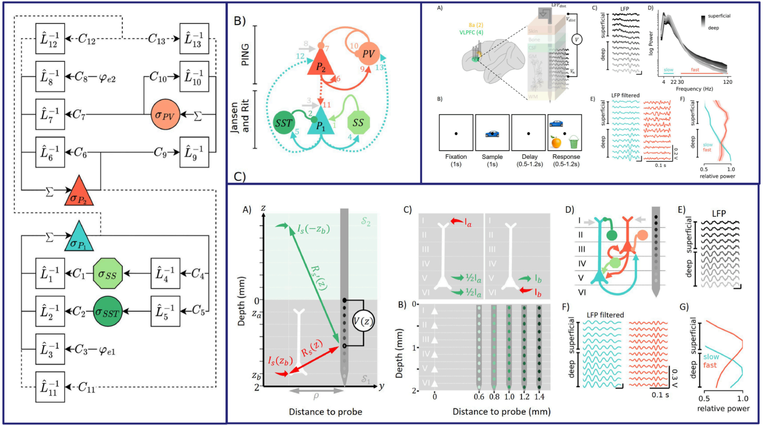
- In 2017, we wanted to build a computational model for AD
- Need: capture two oscillatory features: slowing of EEG, gamma deficit[4;5]. Similar to PD[6].



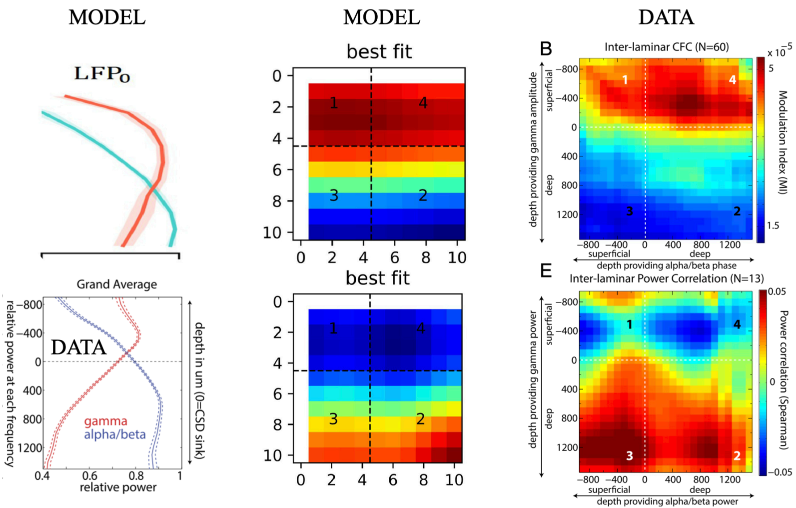


LaNMM Architecture[7]

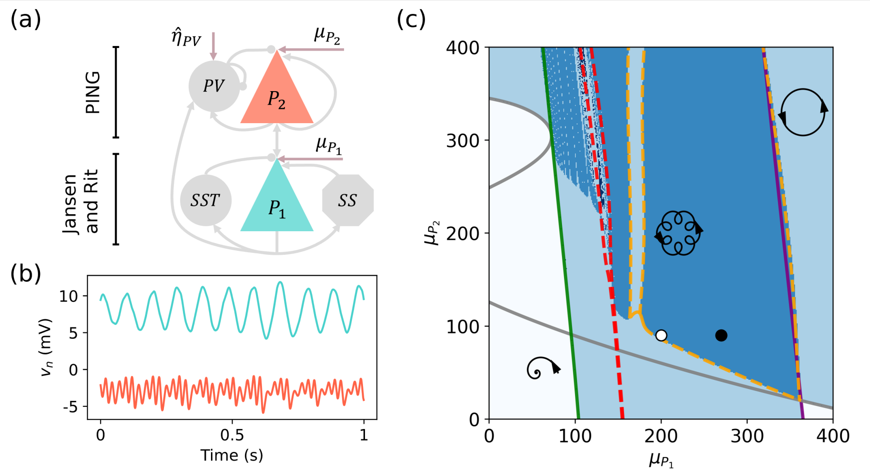
- Biophysical model of a cortical column with laminar (superficial/deep) structure.
- Integrates alpha (slow) and gamma (fast) oscillatory subnetworks.
- Merges Jansen-Rit (alpha) and PING (gamma) models.
- Includes deep/superficial pyramidal cells (P1/P2), inhibitory interneurons (PV), and excitatory stellate inputs.



Model reproduces laminar spectrum and CFC



LaNMM Architecture (Dynamical landscape) (de Palma et al., 2025[8])

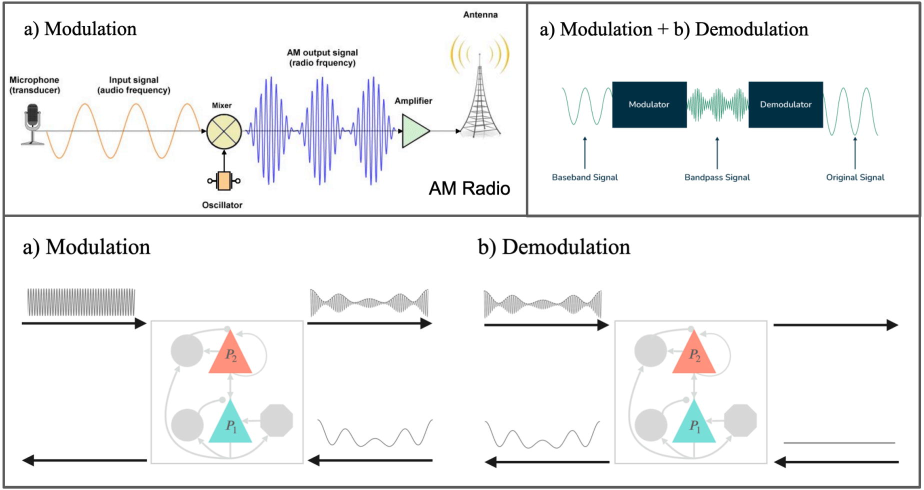


Radios, Information & the Comparator

Where is information encoded?[9]

- Key idea: information is encoded in both neural **signals** and their amplitude **envelopes** (akin to amplitude modulation in radio).
- **Analogy**: a low-frequency signal (message) modulates the amplitude of a high-frequency carrier wave (as in AM radio).
- In the model, the sensory input message is carried in the **envelope** of a fast (γ) signals, and the prediction in the slow (α) one.

AM Radio[9]


a) Modulation
Antenna
AM output signal
(radio frquency)
Microphone
(transducer)
Input signal
(audio frequency)
Mixer
Amplifier
Oscillator
AM Radio
a) Modulation + b) Demodulation
Modulator
Demodulator
Baseband Signal
Bandpass Signal
Original Signal
a) Modulation
b) Demodulation
P_2
P_1
P_2
P_1

Comparator Mechanism (Concept)

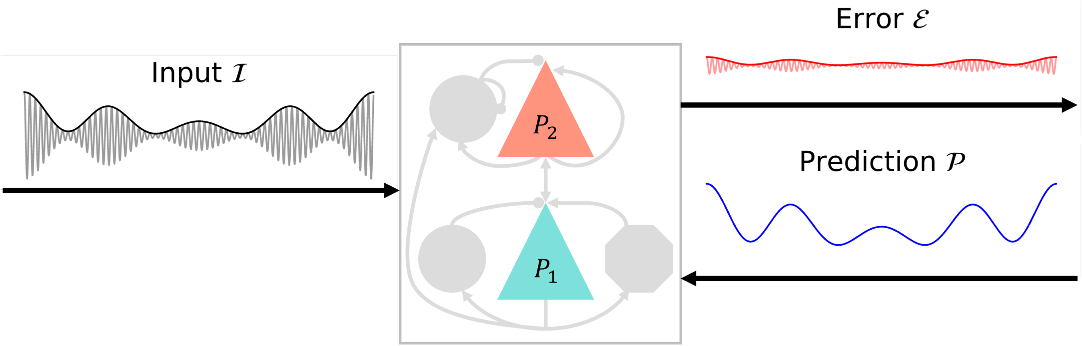
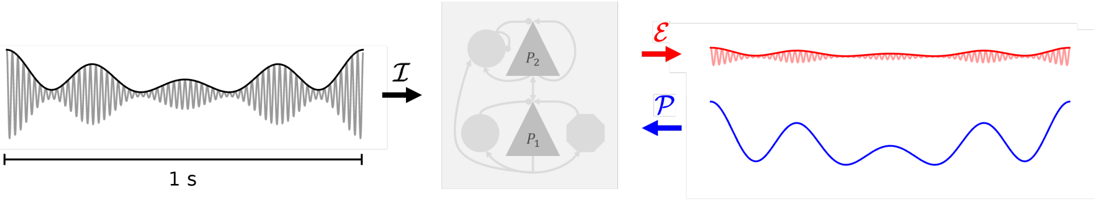


Figure: Conceptual diagram of the Comparator, illustrating how an input $I(t)$ (fast signal + envelope) and a prediction $P(t)$ (slow signal) combine to produce an error signal $E(t)$, with precision signals as envelopes controlling gain

Methods: SEC & EEC

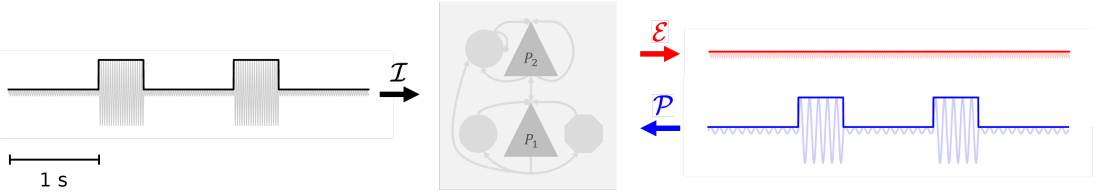
Signal-Envelope Coupling (SEC)

- **SEC:** A low-frequency oscillation modulates the amplitude envelope of a high-frequency oscillation (phase-amplitude coupling of slow and fast rhythms).
- Example: an α wave's phase influences the instantaneous power (envelope) of local γ activity.
- Functional role: SEC enables fast computation of prediction errors by directly injecting slow predictive signals into high-frequency neuronal activity (affecting γ amplitude in real time).

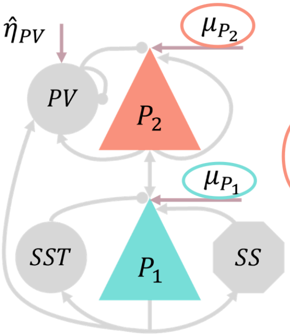


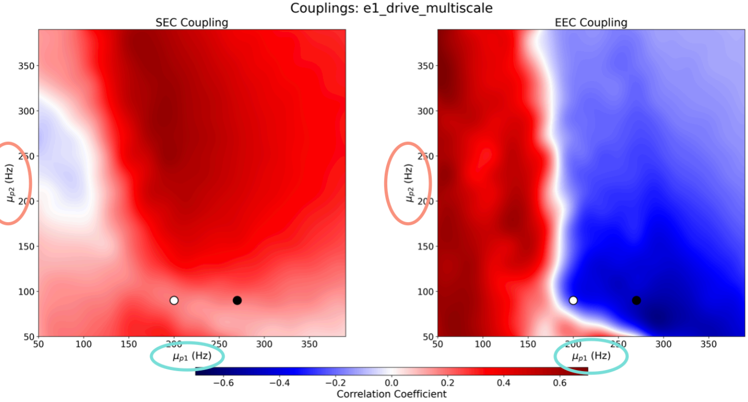
Envelope-Envelope Coupling (EEC)

- **EEC:** The amplitude envelope of a slow oscillation modulates the envelope of a faster oscillation (amplitude–amplitude coupling between frequency bands).
- In other words, a slow modulatory signal (e.g. the envelope of an α/β rhythm) dynamically adjusts the amplitude envelope of γ activity.
- Functional role: EEC implements a **gating mechanism** for precision weighting. The slow envelope encodes precision (confidence), regulating the gain of fast error signals – high precision (strong slow envelope) amplifies error output, low precision attenuates it.

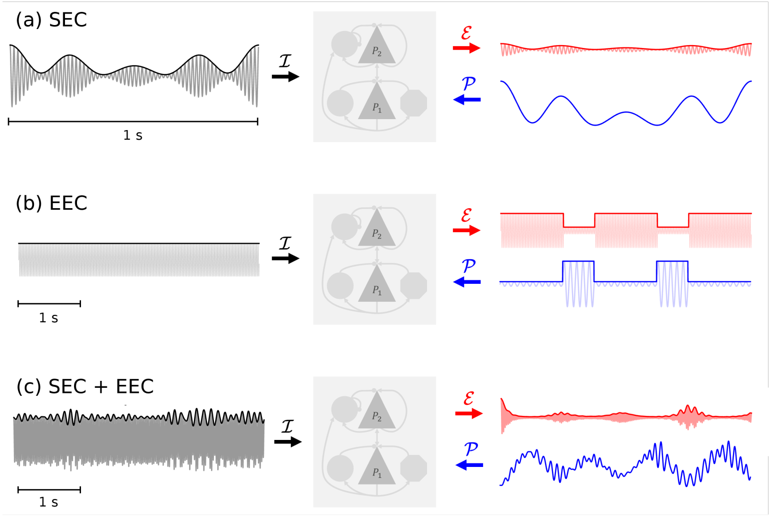


Couplings (P1 drive) (SEC an EEC)





Comparator concept (main idea)



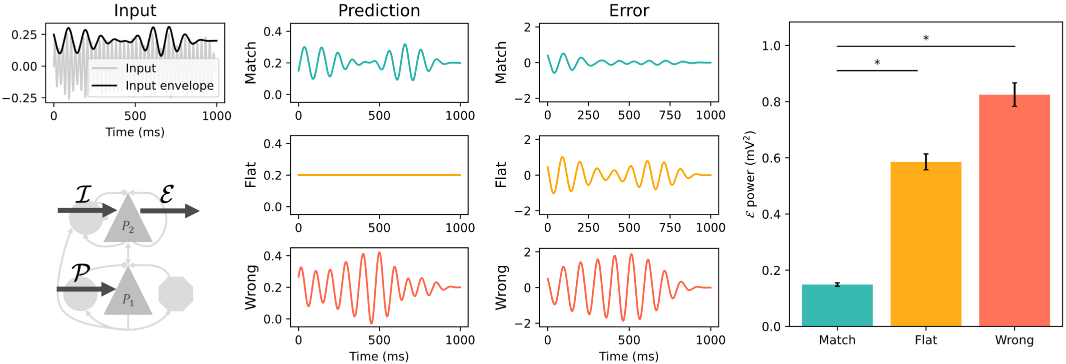
Results: Error Suppression & Modulation

Comparator Simulation (SEC Paradigm)

- Tested the Comparator function by providing synthetic input and prediction signals to the model.
- **Input:** 40 Hz γ carrier oscillation with an α-band (8–12 Hz) envelope (simulated sensory input signal).
- **Prediction:** $\sim$10 Hz α oscillation. Three conditions for the prediction signal: (i) *Match:* envelope matches the input's envelope; (ii) *Flat:* unmodulated flat signal (no envelope); (iii) *Wrong:* an independent (mismatched) α envelope.
- The model's output error signal is measured as the α-band envelope of the P2 (gamma) population output.
- **Hypothesis:** A matching prediction will cancel out the input's envelope, producing a minimal error output, whereas flat or wrong predictions will result in a larger error signal.

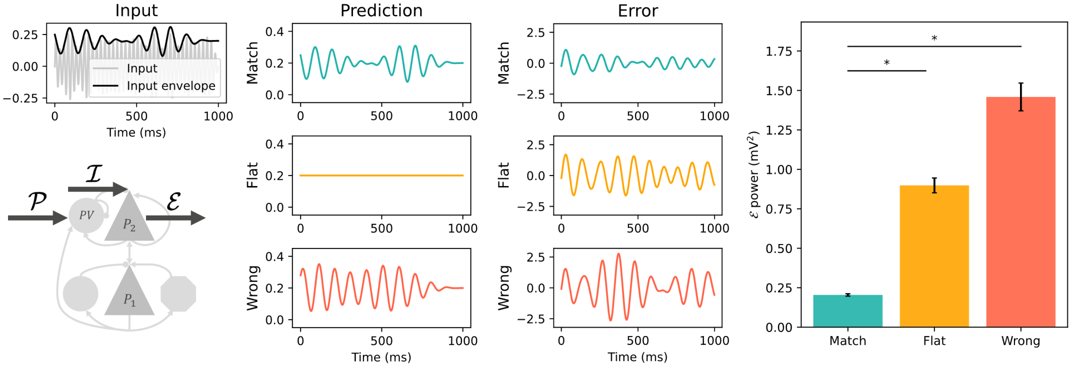
Error Suppression with SEC via P1

- With a matching prediction, the model's error output was drastically suppressed.
- The α-power of the P2 output (error signal) was significantly lower in the *match* condition: a correct top-down prediction effectively "explains away" the bottom-up input.



Error Suppression with SEC via PV

- With a matching prediction, the model's error output was drastically suppressed.
- The α-power of the P2 output (error signal) was significantly lower in the *match* condition: a correct top-down prediction effectively "explains away" the bottom-up input.

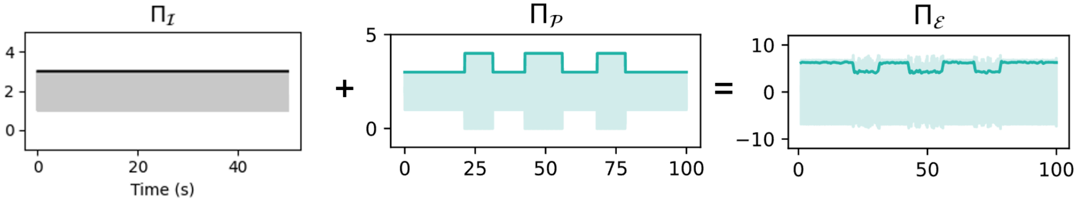


Precision Modulation Simulation (EEC Paradigm)

- Tested precision-weighting by introducing slow envelope modulations representing precision signals.
- **Input precision:** encoded by slow fluctuations in the amplitude of the gamma input's envelope (simulating changes in input reliability over time).
- **Prediction precision:** encoded by a slow envelope applied to the prediction signal (simulating a prior expectation of precision).
- We read out the slow envelope of the P2 output (gamma envelope-of-envelope) as the *error precision* signal.
- **Hypothesis:** The output's slow envelope will approximate the difference between input precision and prediction precision. In other words, the model should subtract the predicted precision from the input precision, implementing proper gating.

Precision gating with EEC

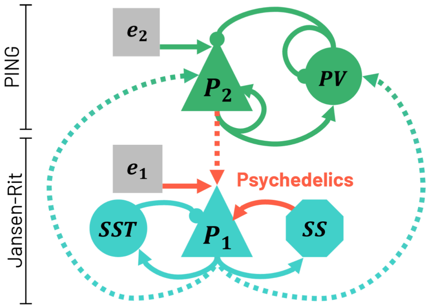
- Introducing a precision-modulating signal to the prediction successfully attenuated the error envelope.
- With a proper precision modulation (versus no modulation), the model's error precision was significantly reduced, confirming that a top-down precision signal can gate (suppress) prediction errors.



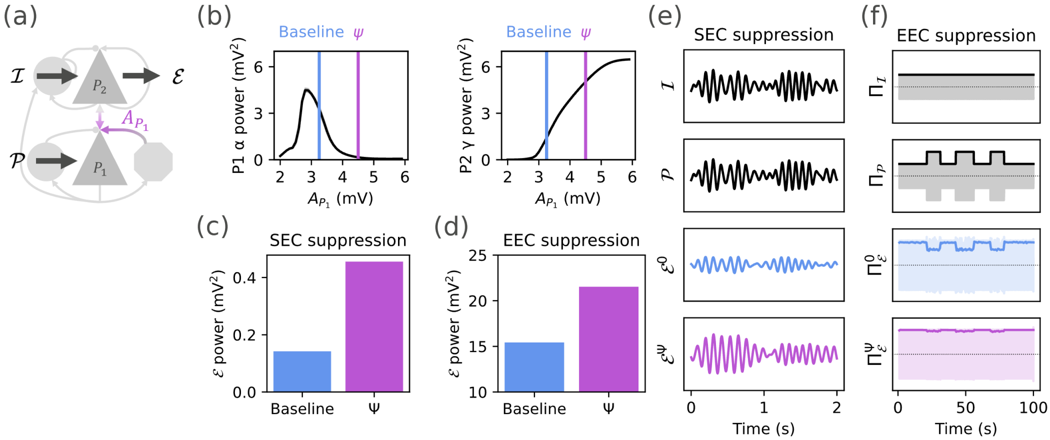
Psychedelics & AD

The Comparator on Psychedelics

- Simulated a psychedelic state by **increasing excitatory gain onto deep pyramidal cells (P1)**, mimicking 5-HT_{2A} agonist effects (increased cortical excitability, Gendra et al., 2025[10].



Effect of Psychedelics

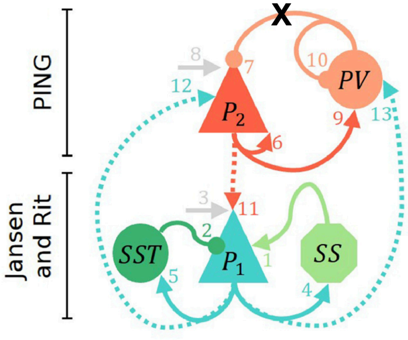


The Comparator on Psychedelics

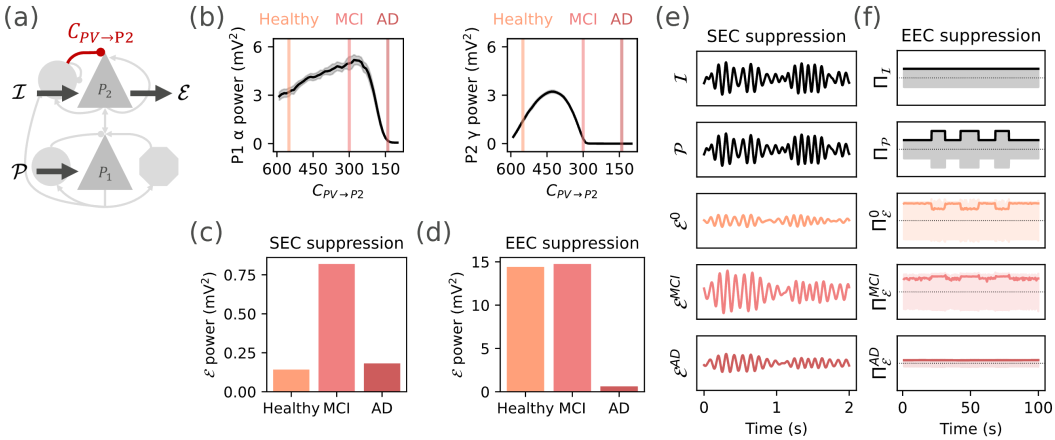
- **Result**: deep-layer α power was markedly reduced, and superficial γ power was elevated (disinhibition of fast activity).
- Even with a matching prediction, the error signal remained abnormally high – the model failed to attenuate prediction errors under this hyper-excitable condition.
- **Interpretation**: Weakened top-down constraints (reduced precision of priors) lead to unfiltered bottom-up signals and excessive prediction errors. This aligns with the REBUS model of psychedelics: **relaxed priors $\rightarrow$ an "anarchic" increase in error signals**.

Perturbation: PV Interneuron Dysfunction (AD Model)

- Simulated Alzheimer's-related inhibitory deficit by reducing the strength of PV interneuron (PV → P2) synapses (disinhibition of P2, Sanchez-Todo et al., 2025[11].



Comparator under PV Dysfunction Perturbation (AD and others)



Perturbation: PV Interneuron Dysfunction (AD Model)

- **Moderate PV loss (early stage):** gamma power increases and prediction error signals are amplified (hyper-excitable cortex with excessive surprise signals).
- **Severe PV loss (late stage):** gamma oscillations collapse into slow-wave dominance (hypoactive cortex), and error signals are greatly attenuated or absent.
- **Interpretation**: Early interneuron dysfunction causes exaggerated prediction errors (**overestimating surprise**), whereas advanced dysfunction leads to a breakdown of error signaling (**failure to propagate errors**).

Final Remarks

Summary I

- We propose an encoding scheme where information is encoded in signals, their envelopes, and envelopes of envelopes.
- We use the LaNMM for a) *Signal-Envelope Coupling (SEC)*, where slow-wave activity modulates the amplitude envelope of fast oscillations, and b) *Envelope-Envelope Coupling (EEC)*, where the envelopes of slower oscillations modulate the envelopes of higher-frequency rhythms.
- We show how to use the LaNMM to implement information-based prediction-error evaluation (as used in Active Inference and Kolmogorov Theory), computing the approximate precision-weighted difference between incoming sensory data (envelopes) and internal model predictions (signals or envelopes).
- Using these mechanisms, the Comparator mechanism can operate at multiple levels and timescales, generating fast prediction-error signals (via SEC) and slower gating signals that encode context (e.g., precision) (via EEC).

Summary II

- In the early stages of AD, error evaluation and precision are disrupted (inflated error and reduced gating/weight of predictions), leading to higher prediction errors. In later stages, prediction errors are suppressed regardless of predictions or their precision.
- Serotonergic psychedelics increase the effective weight of inputs and diminish that of predictions, resulting in higher prediction error signals.
- These observations link oscillatory mechanisms and predictive coding alterations, and potentially with the subjective phenomena in each condition—including cognitive decline in AD and hallucinatory states under psychedelics.

Future Directions

- **Oscillatory computation:** Extend the model to multiple interconnected columns to simulate full hierarchical predictive coding (allowing inter-area prediction and error exchange).
- **I**ncorporate **more realistic** synaptic/connectivity models and receptor-level dynamics to better capture state-dependent changes in precision weighting.
- Investigate **other conditions** with predictive coding abnormalities (e.g. schizophrenia, ASD, ADHD) by examining how their known oscillatory disruptions (e.g. gamma/beta irregularities) fit into this CFC comparator framework.
- **Therapeutic avenues:** Use the model to test interventions (e.g. rhythmic brain stimulation, tACS) aimed at restoring normal cross-frequency coupling and improving predictive processing in disorders.
- Link with Oscillatory Computation research[3].

Closing

- "AM Radio" and CFC provide plausible paradigm for neural computation of prediction errors and their precision weighting.
- Using a laminar cortical model, we showed that distinct modes of coupling – SEC and EEC – can instantiate a Comparator.
- Perturbations of these coupling mechanisms recreated patterns seen in AD and psychedelic states, linking circuit dynamics to cognitive symptoms.
- This work connects predictive coding theory to neurophysiology and neurophenomenology, highlighting how the brain's oscillatory hierarchy might implement inference.

Figure: https://github.com/giulioruffini/SLIDES-Predictive-Coding-Cross-Frequency-BARCCSYN-May-2025

References I

[1] G. Ruffini. An algorithmic information theory of consciousness. *Neurosci Conscious*, 2017. doi: 10.1093/nc/nix019.PMID:30042851.

[2] Giulio Ruffini, Francesca Castaldo, Edmundo Lopez-Sola, Roser Sanchez-Todo, and Jakub Vohryzek. The algorithmic agent perspective and computational neuropsychiatry: from etiology to advanced therapy in major depressive disorder, March 2024. URL `https://osf.io/eqpjh`.

[3] Aida Todri-Sanial, Corentin Delacour, Madeleine Abernot, and Filip Sabo. Computing with oscillators from theoretical underpinnings to applications and demonstrators. *npj Unconventional Computing*, 1(1):1–16, December 2024. ISSN 3004-8672. doi: 10.1038/s44335-024-00015-z. URL `https://www.nature.com/articles/s44335-024-00015-z`. Publisher: Nature Publishing Group.

References II

[4] Emanuel Neto, Elena A. Allen, Harald Aurlien, Helge Nordby, and Tom Eichele. EEG Spectral Features Discriminate between Alzheimer's and Vascular Dementia. *Frontiers in Neurology*, 6, February 2015. ISSN 1664-2295. doi: 10.3389/fneur.2015.00025. URL https://www.frontiersin.org/journals/neurology/articles/10.3389/fneur.2015.00025/full. Publisher: Frontiers.

[5] Elias P. Casula, Maria C. Pellicciari, Sonia Bonnì, Ilaria Borghi, Michele Maiella, Martina Assogna, Marilena Minei, Caterina Motta, Alessia D'Acunto, Francesco Porrazzini, Valentina Pezzopane, Lucia Mencarelli, Andrea Roncaioli, Lorenzo Rocchi, Danny A. Spampinato, Carlo Caltagirone, Emiliano Santarnecchi, Alessandro Martorana, and Giacomo Koch. Decreased Frontal Gamma Activity in Alzheimer Disease Patients. *Annals of Neurology*, 92(3):464, July 2022. doi: 10.1002/ana.26444. URL https://pmc.ncbi.nlm.nih.gov/articles/PMC9543336/.

References III

[6] Giulio Ruffini, David Ibañez, Eleni Kroupi, Jean-François Gagnon, Jacques Montplaisir, Ronald B. Postuma, Marta Castellano, and Aureli Soria-Frisch. Algorithmic complexity of EEG for prognosis of neurodegeneration in idiopathic rapid eye movement behavior disorder (RBD). *Annals of Biomedical Engineering*, 47(1):282–296, August 2018. doi: 10.1007/s10439-018-02112-0. URL `https://doi.org/10.1007/s10439-018-02112-0`. Publisher: Springer Science and Business Media LLC.

[7] Roser Sanchez-Todo, André M. Bastos, Edmundo Lopez-Sola, Borja Mercadal, Emiliano Santarnecchi, Earl K. Miller, Gustavo Deco, and Giulio Ruffini. A physical neural mass model framework for the analysis of oscillatory generators from laminar electrophysiological recordings. *NeuroImage*, 270:119938, April 2023. ISSN 1095-9572. doi: 10.1016/j.neuroimage.2023.119938.

References IV

[8] Raul de Palma Aristides, Pau Clusella, Roser Sanchez-Todo, Giulio Ruffini, and Jordi Garcia-Ojalvo. Emergence of multifrequency activity in a laminar neural mass model. *arxiv*, 2025. tex.affiliation: Department of Medicine and Life Sciences, Universitat Pompeu Fabra, Barcelona, Spain; Department of Mathematics, Universitat Politècnica de Catalunya, Manresa, Spain; Center of Brain and Cognition, Universitat Pompeu Fabra, Barcelona, Spain; Brain Modeling Department, Neuroelectrics, Barcelona, Spain.

[9] Giulio Ruffini and Francesca Castaldo. Neural Encoding through Hiearchical Amplitude Modulation (HAM): a Laminar Neural Mass model implementation ("it is AM radio"). *biorxiv*, 2025.

References V

[10] Jan C. Gendra, Edmundo Lopez-Sola, Francesca Castaldo, Elia Lleal-Custey, Roser Sanchez-Todo, Jakub Vohryzek, Ricardo Salvador, and Giulio Ruffini. Restoring Oscillatory Dynamics in Alzheimer's Disease: A Laminar Whole-Brain Model of Serotonergic Psychedelic Effects, December 2024. URL `https://www.biorxiv.org/content/10.1101/2024.12.15.628565v4`.

[11] Roser Sanchez-Todo, Borja Mercadal, Edmundo Lopez-Sola, Maria Guasch-Morgades, Gustavo Deco, and Giulio Ruffini. Fast Interneuron Dysfunction in Laminar Neural Mass Model Reproduces Alzheimer's Oscillatory Biomarkers, March 2025. URL `https://www.biorxiv.org/content/10.1101/2025.03.26.645407v1`. Pages: 2025.03.26.645407 Section: New Results.