

A Novel Biophysical Whole-Brain Model Explains Power Spectrum Alterations of Serotonergic Psychedelics Using Multimodal Neuroimaging

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Abstract

Background – Psychedelics hold great potential to treat various mental disorders, yet their neurobiological mechanisms remain unclear. Recent mechanistic models have provided valuable insights into the impact of serotonergic psychedelics on brain dynamics. However, these models focus mainly on macroscale brain activity and provide limited information on the psychedelics' mechanisms at the neural population level.

Methods – We provide a novel mechanistic explanation of the well-studied power spectrum alterations in spontaneous cortical activity observed under serotonergic psychedelics, using a physiologically grounded whole-brain model combining multimodal imaging in healthy human participants. Specifically, we combine anatomical data from diffusion magnetic resonance imaging with neurotransmitter data from positron emission tomography of the serotonin 2A receptor (5-HT_{2A}R) density map. Building upon the recent laminar neural mass modelling (LaNMM) framework (Sanchez-Todo et al., 2023), the whole-brain model simulates multiband activity and electrophysiological measurements of the cortical columns, where the 5-HT_{2A}R density controls the average synaptic gain of excitatory connections to layer 5 pyramidal neural populations, rich in 5-HT_{2A}Rs.

Results – Our findings suggest that the decrease in spontaneous cortical oscillatory power in the alpha band and simultaneous increase in the gamma band are mainly influenced by the 5-HT_{2A}R-mediated excitation of deep-layer pyramidal cells. These findings explain the functional effects of 5-HT_{2A}R activation with psychedelics and allow us to propose a novel whole-brain biologically informed explanation for this phenomenon detailed at the mesoscale and based on NMMs.

Perspectives – This model provides valuable insight into the mechanistic underpinnings of psychedelic action in the brain and could be employed to investigate the neuromodulatory potential of psychedelics in re-establishing healthy brain dynamics in mental disorders.

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