Spatial transcriptomics whole-brain modelling explains non-linear functional effects of atomoxetine by a receptor binding affinity principle

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Abstract

Human behavioral repertoire depends on a dynamic reorganization of functional brain activity. Diversity of functional rearrangements is in part enabled by neuromodulatory systems that shape the emergent whole-brain dynamics. Besides, clinical results evidenced neuromodulatory role on health and disease through pharmacological interventions.

Biophysical connectome-based whole-brain models provided mechanistic insights on resting-state large-scale brain dynamics, while pharmacological neuroimaging has been successfully modelled based on the spatial distribution of molecular targets. However, the neuromodulatory phenomena represents a modelling challenge due to the interactions between systems and the functional heterogeneity of receptor subtypes.

Here, we built heterogenous whole-brain network models in which regional excitability is based on neuromodulatory receptor's spatial expression from AHBA. Simulations proved that different perturbations of receptor's expression maps mechanistically explained resting-state fMRI effects from a pharmacological increase of catecholamine levels (i.e., norepinephrine, dopamine).

First, we quantitively describe the differences on static and dynamical connectivity and found that post-atomoxetine (i.e., selective norepinephrine reuptake inhibitor) and post-placebo conditions are significantly different on functional connectivity dynamics ($p<10\text{-}24$, KSD test). We then show that whole-brain network models based on condition-dependent transcriptomics emulated empirical differences. Furthermore, the model in the post-atomoxetine condition predicted a global shift towards critical dynamics. Lastly, we explore the modular structure of receptor spatial similarity networks showing that the differences on receptor influences depend on families of expression patterns. Beyond that, we identified a substantial relationship between receptor-based perturbations and receptor binding affinities, predicting a higher influence of low-affinity receptors under atomoxetine.

In essence, spatial transcriptomics recapitulates a biochemical property of neuromodulatory receptors that bridges large-scale effects of a pharmacological intervention and its molecular mechanism of action. We propose a receptor-based affinity principle as a generic mechanism for large-scale brain reconfigurations, opening a new interpretation of brain dynamics in health and diseases with a direct translation to neuropharmacological development.