IDENTIFYING METABOLIC FLUXES ASSOCIATED WITH LITHIUM RESPONSE IN BIPOLAR DISORDER

Anirudh S. Chellappa[1], Sanjeev Jain[1], Swagatika Sahoo[2,3], Biju Viswanath[1]

[1]*Department of Psychiatry, National Institute of Mental Health & Neuro-Sciences (NIMHANS), Bangalore, India*
[2]*Office of Global Engagement, Indian Institute of Technology Madras, Chennai, India*
[3]*Centre for Integrative Biology and Systems medicinE, Indian Institute of Technology Madras, Chennai, India*

Lithium (Li+) is the most effective drug for bipolar disorder (BD). However, ~40% of patients do not respond. Our incomplete understanding of lithium's mechanisms of action impairs our ability to predict treatment response. There is emerging evidence that Li+ modulates astrocyte metabolism. Because screening for metabolic pathways, in-vivo or in-vitro, is a substantial task, we adopted a computational approach to narrow down towards putative candidates that could be experimentally validated. By integrating publicly-available omics data with human metabolic knowledgebase (Recon3D) we have built genome-scale metabolic models of iPSC-derived astrocytes from BD patients and healthy controls, and explored the metabolic differences in the context of Li+ response. We performed extensive manual curation of literature to capture metabolic tasks and extracellular boundary conditions relevant to astrocytes. The models predicted a reduced flux through the inositol-phosphate cycle specifically in Li+ non-responders, which is in-keeping with the existing literature. The models also predicted a decrease in the flux through mitochondrial fatty acid oxidation, HMGCoA-synthesis and endoplasmic reticulum (ER) cholesterol pathways, specifically in non-responders. The question of whether these fluxes are disrupted in BD patients' astrocytes and restored upon Li+ treatment, leading to a clinical response, remains open and is being investigated using appropriate experimental model systems. More generally, our computational framework provides a platform to integrate multi-omics data and explore the effects of genetic and pharmacological perturbations on cellular metabolism.