

Title: Computational modelling of brain energy metabolism in schizophrenia

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Abstract

Schizophrenia is a highly heritable psychiatric disorder characterized by diverse symptoms such as hallucinations, delusions, lack of pleasure, and cognitive deficits. Although its etiology remains unclear, converging evidence suggests disturbances in several biochemical pathways of the brain, including brain energy metabolism, whose precise activity is essential for neuronal signaling. The relationship between genetic alterations and energy metabolism, however, is poorly understood. Thus, we combined differential expression (DE) analysis with computational modelling to investigate how the expression of cytosolic energy metabolism genes influences the concentrations of central energy metabolites. The DE analysis was performed using human post-mortem RNA sequencing data from the anterior cingulate cortex (ACC) and prefrontal cortex (PFC). We conducted both population-average and subject-specific (personalized) simulations with a biophysical model of brain energy metabolism developed by Winter et al. (2018).

The DE analysis identified nine genes in the ACC and 24 in the PFC. Around two thirds of the DE genes were downregulated in schizophrenia in both brain areas. The simulation results showed that altered expression of a single gene had no significant effects on the metabolite concentrations in most cases. However, decreased expression of neuronal *LDHB* in the ACC significantly altered a few neuronal metabolites. Additionally, decreased expression of neuronal *PFKM* in the PFC caused significant alterations in almost all studied metabolites in both neurons and astrocytes. These findings provide further evidence for region-specific dysregulation of brain bioenergetics in schizophrenia and suggest mechanistic links between gene expression changes and altered levels of key metabolites.