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CLEVER

Rebalancing gluCOse utilization in vulnErability to chronic stress: a nOvEl stratEgy to promote Resiliency against psychopathology

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The lifetime prevalence (~20%) and economic burden (\$350 billion annually) associated with major depressive disorders (MDD) make them one of the most common and debilitating psychiatric illnesses. Currently, the diagnosis of MDD and suicidal behaviors are subjective and quantitative biomarkers for early detection and long-term assessment are lacking. Without such objective biomarkers, diagnosis, monitoring and treatment adjustments rely exclusively on suboptimal clinical examination.

We hypothesize that regional changes of brain activity linked to MDD reflect the utilization of distinct fuel sources for its metabolism. Specifically, we propose that MDD patients rely more on lipids than carbohydrates to meet energy demands, whereas successful treatment would reduce lipolysis and promote glycolysis.

The primary objective of the project is to discover genes and pathways with high relevance for individuals that are more vulnerable to MDD and insufficient treatment response. The secondary objective is to exploit the candidate genes and pathways as proof-of-concept to restore fuel utilization

towards more carbohydrates and less lipids in the brain of preclinical animal models of MDD.

The project is designed as a reverse translation from patients to animal models and back with a proof-of-concept for intervention. The project will provide conceptual advance in normal and dysfunctional brain/body metabolism, paving the way for predictive metabolic representations of trajectories to successful treatment and prevention. It will also provide novel targets for therapeutic intervention that could significantly improve the quality of life of the affected individuals and their families.

