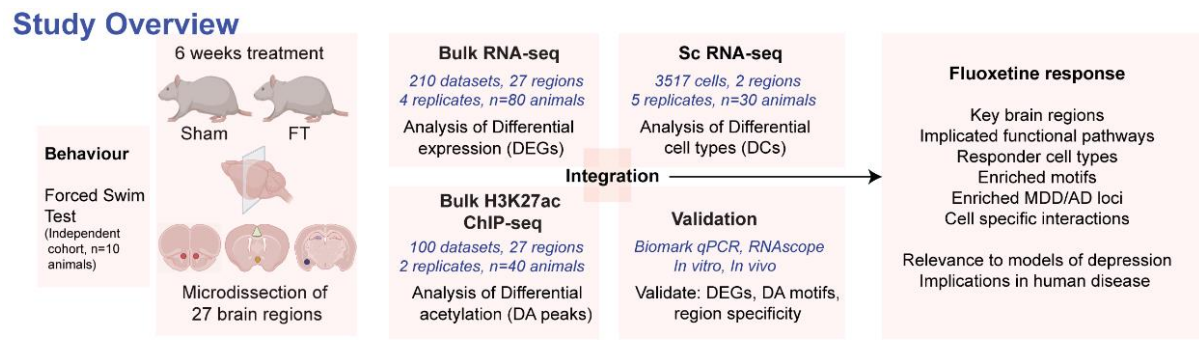
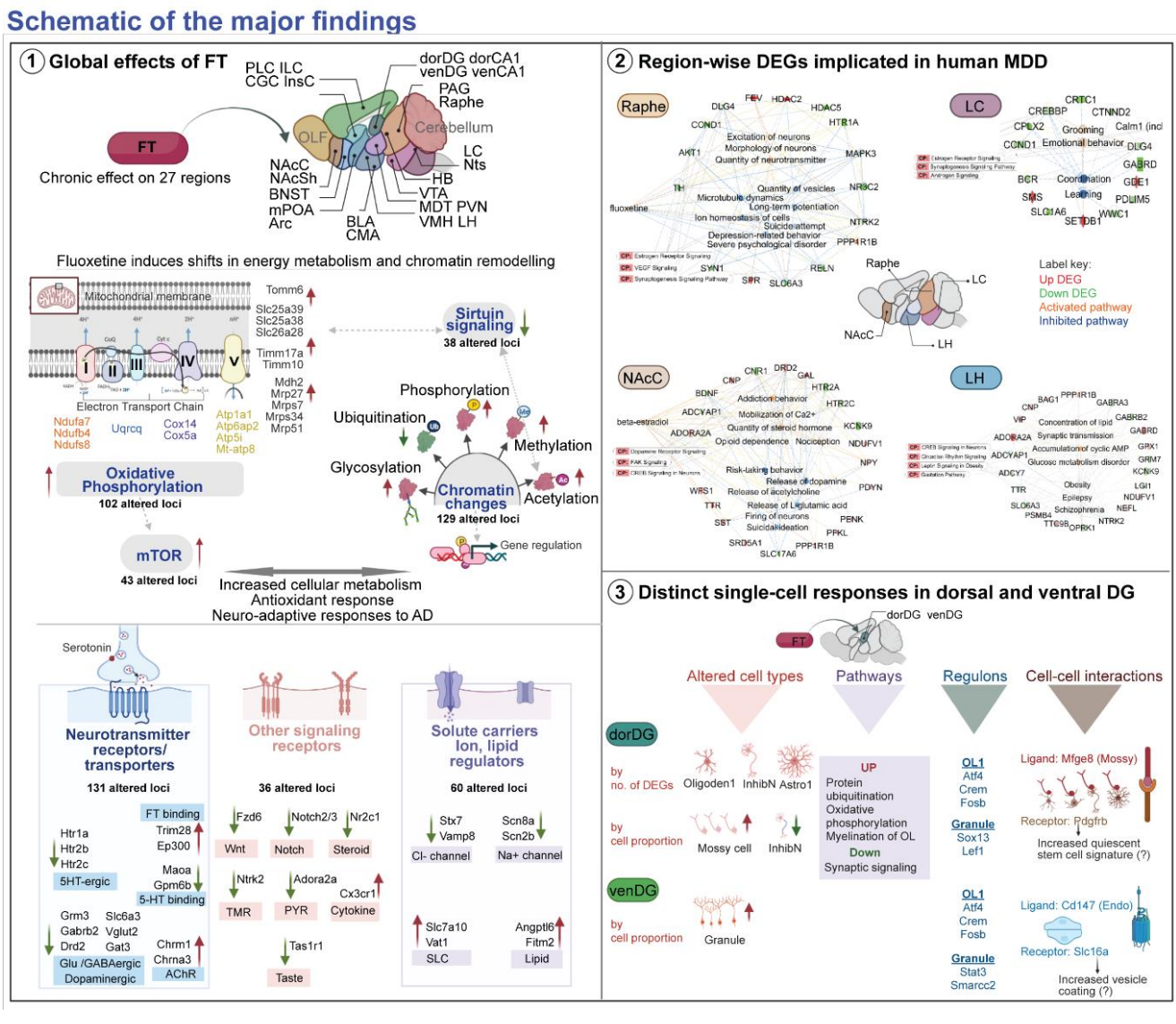
THE BRAIN ON HAPPY PILLS: HOW PROZAC CHANGES THE RNA, DNA PACKAGING AND CELLS IN DIFFERENT BRAIN AREAS





20 September 2022 – Depression ranks among the top causes of morbidity and mortality worldwide. The COVID-19 pandemic has considerably worsened this global public health burden by triggering a dramatic three-fold increase in prevalence across 200 countries. Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine (FT, brand name: Prozac) are a class of antidepressant drugs routinely prescribed for depression, panic attacks, and obsessive-compulsive disorder, including some non-psychiatric conditions. However, the responses to SSRI medications vary from person to person, with some people having substantial side effects like mental sluggishness, sexual dysfunction and increased suicidality. These indicate that the drug effects are complex and likely affect multiple brain regions.

Researchers have long used rats and mice to understand how antidepressants act and rescue animals from symptoms of depression and anxiety. The research team used high-throughput genomic technology to map out all Prozac-induced changes to the RNA content and DNA packaging within the brain cells of 27 rat brain regions. They revealed that thousands of genes turned on and off in response to fluoxetine across the 27 brain areas. They also found that the DNA of fluoxetine-treated brains had different acetylation levels (resulting in the opening or closing of DNA packaging). This gave the researchers an idea of the most affected brain region and an unbiased, complete map of all changes happening in these small brain areas.

The study revealed that Prozac (fluoxetine) impacted the brain in two broad themes. Firstly, fluoxetine increased energy production in almost all 27 regions (a global mechanism of fluoxetine action). Since depression is associated with lower energy levels in the brain, this could constitute a fundamental mechanism by which fluoxetine exerts its therapeutic effect. In contrast, communication between brain cells, transport of cargo and DNA packaging were region-specific, suggesting multiple additional mechanisms that vary from one brain area to another.

Next, the researchers used single-cell technology to identify which cells (various types of neurons and glial cells, among others) experience the above changes. They examined thousands of single cells in two hippocampus brain regions and identified specific cell classes most responsive to fluoxetine.

"The dataset generated from this study will provide the psychiatric research community with a much-needed framework to select brain regions, gene candidates and pathways for further in-depth studies. For example, specific candidate genes identified in this study could underlie alterations in sleep patterns and pain perception observed upon long-term use of SSRI antidepressants. "

Dr Shyam Prabhakar, Senior Group Leader,
Laboratory of Systems Biology and Data Analytics,
and Associate Director, Spatial and Single Cell Systems, GIS

"Prozac turns multiple light bulbs (genes) on and off by flipping switches (gene regulators). This work captures all such effects in cells of multiple rat brain areas."

Dr Nirmala Arul Rayan, first author of the study,
and Senior Programme Manager,
Laboratory of Systems Biology and Data Analytics, GIS

"Depression is a debilitating condition that can critically impact a person's daily functioning to the extent of suicide. This study used bulk and single-cell omics to examine Prozac's effect with a magnifying glass to better understand depression and how antidepressants work. It provides an atlas of molecular (RNA levels, DNA packaging) and cellular changes caused by fluoxetine in 27 brain regions. Future studies could eventually improve and refine therapeutic development for depression and anxiety."

Prof Patrick Tan, Executive Director, GIS

The research was published in *Molecular Psychiatry* on 2 September 2022.