

Upgrade Proposal

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Background

Summary of current state of the field and context within which the research is located, covering current theory/state of the evidence and referring to relevant literature (500-1,000 words).

The NMDA hypofunction hypothesis of schizophrenia proposes that decreased activity of NMDA receptors has a key role in the development of schizophrenia pathology. The affected NMDA receptors are primarily localised at GABA-ergic fast-spiking PV interneurons; where decreased activity of PV interneurons causes a disinhibition of their activity on pyramidal neurons, disrupting the EI balance, and leading to increased excitation. Hyperactivity in the hippocampus is observed in the early stages in schizophrenia, as well as in people at clinical high risk of schizophrenia that subsequently develop the disorders, suggesting this region might be implicated in the development of the pathology at early stages of the disorder. This is consistent with the observations that administration of NMDA antagonists like phencyclidine and ketamine induces behaviours comparable to all three schizophrenia symptom dimensions (positive, negative, and cognitive symptoms) (citations from¹), and repeated administration results in increased release of DA in rodent striatum citations from¹, suggesting that hyperdopaminergia is caused by decreased NMDA activity^{2,3}.

Alterations in synaptic function have also been implicated in the aetiology of schizophrenia⁴. Excitotoxicity caused by increased glutamatergic activity might be one of the contributing factors in the reduction in synaptic connections in schizophrenia. Postmortem studies have reported decreased⁵

Aims and objectives

- The aim of my project is to examine the relationship between synaptic connectivity and glutamatergic function. To do this I will measure the difference in glutamate levels (MRS) after administration of LEV and placebo in healthy controls and people with schizophrenia.
- The recruitment target is 50 participants: 25 healthy controls (HC) and 25 people with schizophrenia (SZ).

Hypotheses under investigation

I will aim to answer the following questions:

1. Does modulating SV2A lead to lower glutamate levels in healthy people?
2. Does modulating SV2A lead to lower glutamate levels in people with schizophrenia? Is the change different to that in healthy controls?
3. Does modulating SV2A lead to change in symptoms in schizophrenia?

Methodology

Study design and data collection

- Single-blind, randomised, placebo-controlled trial with cross-over design.

Analysis

- MRS data processing with Osprey - Hippocampus and ACC SVS

Statistics

- Statistical analysis: ANOVA / t-test (within and between group). Power calculations.
- I will compare the effect of levetiracetam on Glx levels in healthy controls (HC) and patients with schizophrenia (SZ). This will be visualised on a raincloud plot such as the one below. The data used in this graph is made up for the purpose of illustrating the types of comparisons and data visualisations I plan on using.

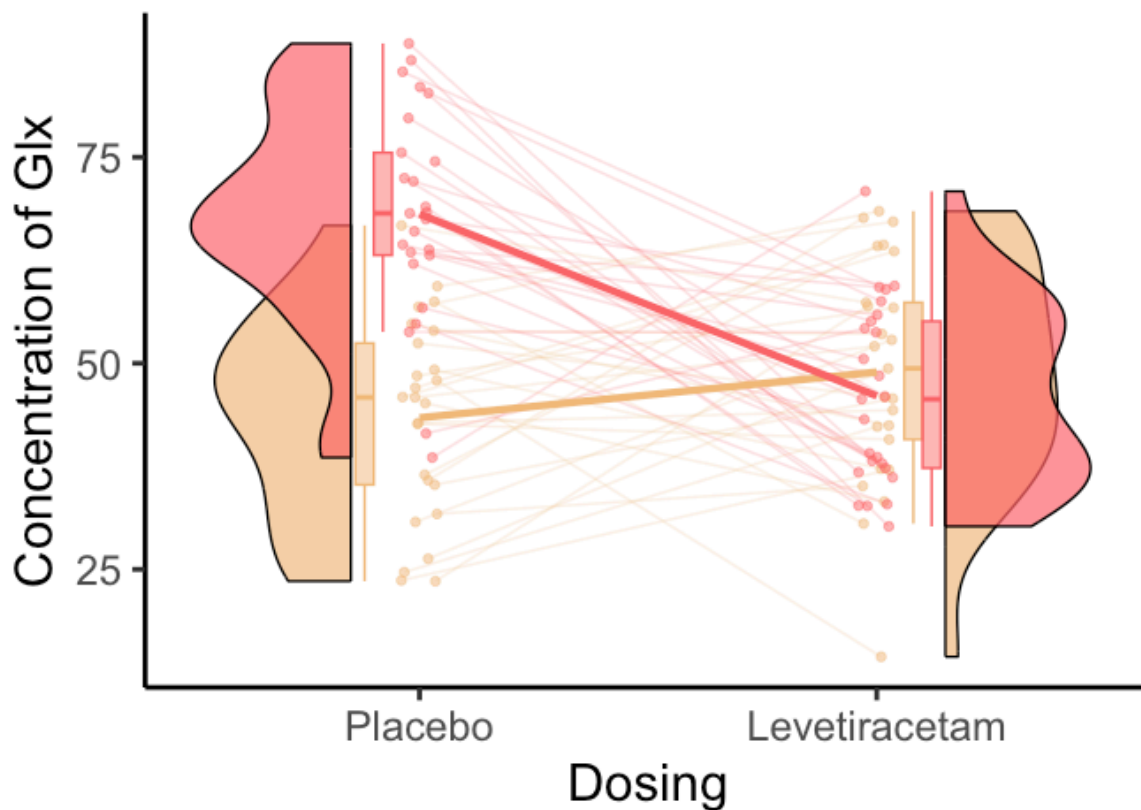


Figure 1: Comparison of GLX levels change between placebo and levetiracetam in HC and SZ

Source: [Plots](#)

Progress made to date, including pilot work, if applicable

Planned future work

Contribution to existing knowledge.

How the research will form a distinct contribution to existing knowledge on the subject and afford evidence of originality shown by discovery of new facts or exercise of independent critical power

Personal share in investigations

Where work is done in conjunction with the supervisor and/or with collaborators or other students, a statement of the candidate's own personal share in the investigations

Timeline for the remainder of studies.

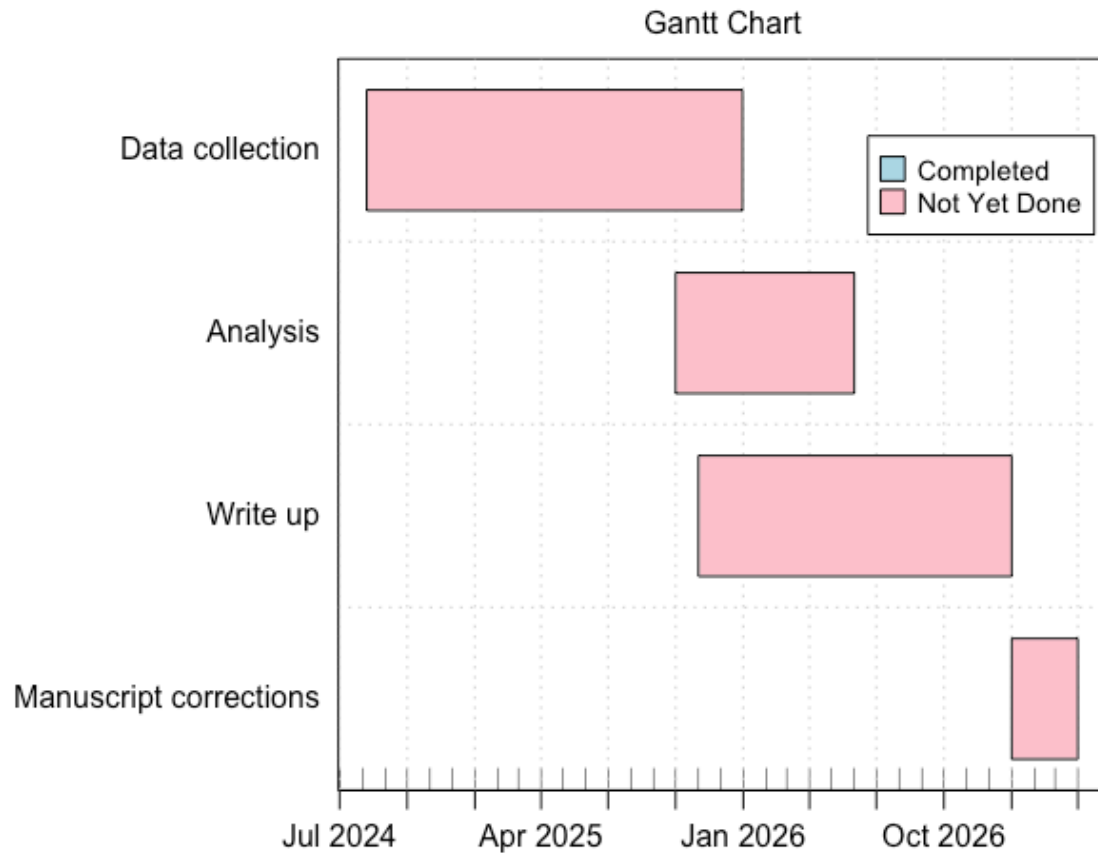


Figure 2: Gantt chart of planned work during my PhD

Source: [Plots](#)

References

1. Nakazawa, K. & Sapkota, K. The Origin of NMDA Receptor Hypofunction in Schizophrenia. *Pharmacology & Therapeutics* **205**, 107426. ISSN: 01637258. <https://linkinghub.elsevier.com/retrieve/pii/S0163725819301780> (Jan. 2020).
2. Grace, A. A. Dopamine System Dysregulation by the Hippocampus: Implications for the Pathophysiology and Treatment of Schizophrenia. *Neuropharmacology* **62**, 1342–1348. ISSN: 00283908. <https://linkinghub.elsevier.com/retrieve/pii/S0028390811001912> (Mar. 2012).
3. Grace, A. A. Dysregulation of the Dopamine System in the Pathophysiology of Schizophrenia and Depression. *Nature Reviews Neuroscience* **17**, 524–532. ISSN: 1471-003X, 1471-0048. <https://www.nature.com/articles/nrn.2016.57> (Aug. 2016).
4. Howes, O. D. & Onwordi, E. C. The Synaptic Hypothesis of Schizophrenia Version III: A Master Mechanism. *Molecular Psychiatry*. ISSN: 1359-4184, 1476-5578. <https://www.nature.com/articles/s41380-023-02043-w> (Apr. 11, 2023).
5. Abdallah, C. G. *et al.* The Effects of Ketamine on Prefrontal Glutamate Neurotransmission in Healthy and Depressed Subjects. *Neuropsychopharmacology* **43**, 2154–2160. ISSN: 0893-133X, 1740-634X. <http://www.nature.com/articles/s41386-018-0136-3> (Sept. 2018).