# Analysis Plan

Title: Lithium and Atypical Antipsychotics in Bipolar Disorder: Self-Harm, Suicidality, and Brain Volumes

Researcher: Jamie Hounsell

Approvers: Olivia Harrison and Bruce Russell

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**Foreword:**

This project aims to analyse information on self-harm behaviours and brain MRI data, sourced from the UK Biobank, of subjects diagnosed with bipolar disorder, as well as a healthy control group. Four our behavioural analysis we will compare data from the UK Biobank on bipolar patient self-harm and suicidal behaviours between a lithium group and an atypical antipsychotic group. For our MRI analysis, comparisons between those with bipolar disorder taking lithium versus those taking an atypical antipsychotic will be made, and against the control group, focussing on grey matter volumes. The dataset of this project comes from the results of T1-weighted brain MRI IDP volumes, as well as subject demographics and medical history information. This project will occur within a larger study conducted by the Otago School of Pharmacy concerning the long-term effects of psychiatric drugs on brain structure, function, and cognition.

This analysis plan aims to briefly outline the intended project, with background of the topic, research questions and hypotheses, and planned analysis.

**Introduction:**

Bipolar disorder is a lifelong chronic mood disorder characterised by manic or hypomanic episodes alternating with depressive episodes (Grande et al., 2016). Affecting over 1% of the global population, bipolar disorder is a leading cause of disability in youth, with an extremely high risk of suicide wherein it is estimated that up to half of people with bipolar disorder attempt suicide at least once in their lives (Grande et al., 2016). Treating bipolar disorder focuses on stabilising the patient from a manic or depressive episode to a euthymic state, and maintenance to prevent relapse and improve occupational and social functioning- this involves a combination of pharmacological and psychological treatment (Geddes & Miklowitz, 2013). Lithium is a drug that is specifically used for bipolar disorder (Geddes & Miklowitz, 2013). Lithium works at multiple sites in the brain to provide mood stabilisation (Jope, 1999) and is effective in preventing depressive and manic episodes (Grande et al.,

2016). Antipsychotics are effective for treating mania and have a faster or larger response than lithium (Yildiz et al., 2011). Quetiapine, an atypical antipsychotic, is effective as both an antipsychotic, antimanic, and antidepressant, and has a larger effect on symptomatic improvement in bipolar depression, which is an especially difficult aspect of the disease to treat (Grande et al., 2016). This project aims to compare lithium and atypical antipsychotics to see if they correlate with differences in self-harm behaviours and brain structure in bipolar disorder. By utilising UK Biobank data, a selection of atypical antipsychotics can be investigated with sample sizes larger than some previous studies and allow extra exploratory questions to be investigated. This project will look at T-1 weighted MRI data of cortical and subcortical brain structures, and information on patient history's of self-harm and suicide.

**Research Questions and Hypotheses**

Experimental Question 1: Is there a difference between those with bipolar disorder taking lithium versus atypical antipsychotics in both suicidality and self-harm behaviours?

- We will compare those taking lithium and those taking an atypical antipsychotic of interest and their biobank data that indicates their history of self-harm, and if they have ever attempted suicide.

  Hypothesis 1: There will not be a difference between lithium and atypical antipsychotics and the number of times they have self-harmed, nor a difference between these groups and if they have ever attempted suicide (Hayes et al., 2016).

Experimental Question 2: Are there differences in grey matter between those with bipolar disorder taking lithium compared to atypical antipsychotics?

- We will compare grey matter volumes between three groups: those with bipolar disorder taking lithium, those with bipolar disorder taking an atypical antipsychotic of interest, and neurologically healthy age matched controls. The antipsychotics that this project will look at are quetiapine, olanzapine, and risperidone.

  Hypothesis 2: Those taking atypical antipsychotics will show regional effects on brain structure, especially in the thalamus,(Birner et al., 2020) and that those taking lithium

will show more global effects on the brain (i.e. will show increased total grey matter) (Germana et al., 2010).

## Dataset

To investigate our research questions, we will utilise data from the UK Biobank dataset aims to image 100,000 participants. This dataset includes MRI neuroimaging as well as subject demographics and medical information of subjects aged 40-69 years old when recruited between 2006-2010 (Sudlow et al., 2015). We will use subjects who have T1 MRI structural data, and subsequently select a subset of those with a diagnosis of bipolar disorder. From the bipolar group there will be two further subgroups; those who have been prescribed lithium, and those who have been prescribed at least one of the selected atypical antipsychotics (quetiapine, olanzapine, and risperidone). As well as this there will be an age and gender matched healthy control group.

*Exclusion of datasets*

Reasons for excluding data sets are:

- Missing MRI data
- Those taking both lithium and an atypical antipsychotic

## Analysis

*IDP analysis*

Choice of IDPs:

Cortical Grey Matter IDPs

| **IDP** | **Volume of Grey Matter** |
|---|---|
| 25005 | Volume of grey matter (normalised for head size) |
| 25006 | Volume of grey matter |
| 25782 | Volume of grey matter in Frontal Pole (left) |
| 25783 | Volume of grey matter in Frontal Pole (right) |
| 25784 | Volume of grey matter in Insula Cortex (left) |
| 25785 | Volume of grey matter in Insula Cortex (right) |
| 25786 | Volume of grey matter in Superior Frontal Gyrus (left) |
| 25787 | Volume of grey matter in Superior Frontal Gyrus (right) |
| 25788 | Volume of grey matter in Middle Frontal Gyrus (left) |
| 25789 | Volume of grey matter in Middle Frontal Gyrus (right) |
| 25794 | Volume of grey matter in Precentral Gyrus (left) |
| 25795 | Volume of grey matter in Precentral Gyrus (right) |
| 25838 | Volume of grey matter in Cingulate Gyrus anterior division (left) |
| 25839 | Volume of grey matter in Cingulate Gyrus anterior division (right) |

| | |
|---|---|
| 25840 | Volume of grey matter in Cingulate Gyrus posterior division (left) |
| 25841 | Volume of grey matter in Cingulate Gyrus posterior division (right) |
| 25798 | Volume of grey matter in Superior Temporal Gyrus anterior (left) |
| 25799 | Volume of grey matter in Superior Temporal Gyrus anterior (right) |
| 25800 | Volume of grey matter in Superior Temporal Gyrus posterior (left) |
| 25801 | Volume of grey matter in Superior Temporal Gyrus posterior (right) |
| 25802 | Volume of grey matter in Middle Temporal Gyrus anterior (left) |
| 25803 | Volume of grey matter in Middle Temporal Gyrus anterior (right) |
| 25804 | Volume of grey matter in Middle Temporal Gyrus posterior (left) |
| 25805 | Volume of grey matter in Middle Temporal Gyrus posterior (right) |
| 25806 | Volume of grey matter in Middle Temporal Gyrus temporooccipital (left) |
| 25807 | Volume of grey matter in Middle Temporal Gyrus temporooccipital (right) |
| 25808 | Volume of grey matter in Inferior Temporal Gyrus anterior (left) |
| 25809 | Volume of grey matter in Inferior Temporal Gyrus anterior (right) |
| 25810 | Volume of grey matter in Inferior Temporal Gyrus posterior (left) |
| 25811 | Volume of grey matter in Inferior Temporal Gyrus posterior (right) |
| 25812 | Volume of grey matter in Inferior Temporal Gyrus temporooccipital (left) |
| 25813 | Volume of grey matter in Inferior Temporal Gyrus temporooccipital (right) |
| 25814 | Volume of grey matter in Postcentral Gyrus (left) |
| 25815 | Volume of grey matter in Postcentral Gyrus (right) |
| 25818 | Volume of grey matter in Supramarginal Gyrus anterior (left) |
| 25819 | Volume of grey matter in Supramarginal Gyrus, anterior division (right) |
| 25820 | Volume of grey matter in Supramarginal Gyrus, posterior division (left) |
| 25821 | Volume of grey matter in Supramarginal Gyrus, posterior division (right) |
| 25824 | Volume of grey matter in Lateral Occipital Cortex, superior division (left) |
| 25825 | Volume of grey matter in Lateral Occipital Cortex, superior division (right) |
| 25826 | Volume of grey matter in Lateral Occipital Cortex, inferior division (left) |
| 25827 | Volume of grey matter in Lateral Occipital Cortex, inferior division (right) |
| 25830 | Volume of grey matter in Frontal Medial Cortex (left) |
| 25831 | Volume of grey matter in Frontal Medial Cortex (right) |
| 25836 | Volume of grey matter in Paracingulate Gyrus (left) |
| 25837 | Volume of grey matter in Paracingulate Gyrus (right) |
| 25842 | Volume of grey matter in Precuneous Cortex (left) |
| 25843 | Volume of grey matter in Precuneous Cortex (right) |
| 25844 | Volume of grey matter in Cuneal Cortex (left) |
| 25845 | Volume of grey matter in Cuneal Cortex (right) |
| 25870 | Volume of grey matter in Heschl's Gyrus (includes H1 and H2) (left) |
| 25871 | Volume of grey matter in Heschl's Gyrus (includes H1 and H2) (right) |

Subcortical IDPs

| **IDP** | **Volume** |
|---|---|
| 25878 | Volume of grey matter Thalamus (left) |
| 25879 | Volume of grey matter Thalamus (right) |
| 25880 | Volume of grey matter Caudate (left) |
| 25881 | Volume of grey matter Caudate (right) |
| 25882 | Volume of grey matter Putamen (left) |
| 25883 | Volume of grey matter Putamen (right) |

| | |
|---|---|
| 25884 | Volume of grey matter Pallidum (left) |
| 25885 | Volume of grey matter Pallidum (right) |
| 25886 | Volume of grey matter Hippocampus (left) |
| 25887 | Volume of grey matter Hippocampus (right) |
| 25888 | Volume of grey matter Amygdala (left) |
| 25889 | Volume of grey matter Amygdala (right) |

*Group comparison tests:*

Research Question 1: Differences in self-harm behaviours between the lithium and atypical antipsychotic groups will be analysed with Chi-Squared tests.

Research Question 2: Group differences between selected IDPs will be analysed with a three-by-one way ANOVA, with post-hoc tests to compare differences between the groups.

*Correction for multiple comparisons:*

The significant value of $p<0.05$ will be used in the initial ANOVA tests.

**Possible extensions and modifications**

If time and subject numbers permit, analysis of DTI data may be used in the same manner to examine changes in white matter between lithium and atypical antipsychotics in bipolar disorder.

**References**


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