Analysis plan

Title:	Investigating SSRI use in alcohol addiction; is it worth a shot?
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Approved by:	Associate Professor Bruce Russell
Date:	24 August, 2022

Foreword

This document contains the analysis plan for the project entitled 'Investigating SSRI use in alcohol addiction; is it worth a shot?'

The wider project concerns the analysis of the use of pharmacotherapies to treat mental health disorders, conducted at the School of Pharmacy (University of Otago). This project is focussed on the use of medication to help treat alcohol addiction, and the impact that this therapy may have on brain structure. The study contains data from approximately 178 participants, all of whom have suffered with alcohol addiction in their past and approximately 89 of whom have additionally taken specific selective serotonin reuptake inhibitors (SSRIs). Data from these participants were collected through the UK Biobank, which we have been granted access to for the completion of this study. The data analysed in this study will be various grey matter brain regions from structural magnetic resonance images, and whether participants continue to have an addiction to alcohol.

The purpose of this analysis plan is to provide a brief rationale for the proposed study, formulate the experimental questions and hypotheses, and describe statistical measures and post-hoc testing with rationale for each step required. All code used in this project will be documented on the internal GitHub page (https://github.com/IMAGEotago) of the IMAGE Otago research group.

Introduction

Alcohol use disorder (AUD) affects an estimated 300 million people, and is the cause of approximately 5.3% of deaths worldwide (addictioncentre.com). Despite this prevalence, there are very limited treatment options available. The most common pharmacological treatment – disulfiram—causes any ingestion of alcohol to be intolerable, and causes severe nausea and vomiting (Zindel & Kranzler, 2014). There are behavioural alternatives such as alcoholics anonymous, which focus on growth of support networks and change in beliefs surrounding alcohol. These treatment options are either largely unsuccessful or inaccessible, evident by the number of people who continually have an AUD. Therefore, more research is required for alternative interventions with less severe side effects than disulfiram.

One such intervention may be a small range of selective serotonin reuptake inhibitors (SSRIs). Kobayashi et al., (1999) found that alcohols such as ethanol directly open g-protein coupled inwardly rectifying potassium channels (GIRK), and cause decreased neurotransmission, which may be a mechanism of intoxication. Later, Aryal et al., (2009) identified GIRK's alcohol binding pocket in mice. Furthermore, Kobayashi et al., (2004) continued their studies on GIRK, and found that several SSRIs including fluoxetine and paroxetine bind to GIRK with an antagonistic effect, causing less activity of these channels.

This research has been paired with numerous behavioural studies over the years. Mayfield et al., (2015) noted that GIRK3 subunit knockout mice reduced their free ethanol drinking behaviour, and lessened their severity from alcohol withdrawal than wildtype mice. Some human studies have also found that those taking SSRIs like fluoxetine, citalopram, and fluvoxamine may reduce drinking behaviour, although there are also many lifestyle factors which may cause confounds (Naranjo et al., 2001). These studies potentially highlight the same underlying mechanism of alcohol use disorder, and that inhibition of GIRK activity (whether through knockouts or SSRI treatment) may cause a decrease in 'desire' to drink alcohol.

To date, nobody has investigated whether these SSRIs cause structural changes in the brain in the context of AUD, and how this may be linked to recovery from addiction behaviours. These changes may occur in areas associated with high GIRK channel localisation, or areas commonly affected with AUD. Therefore, this study will use structural MRI data from the UK Biobank, to investigate whether use of fluoxetine, paroxetine, citalopram, and sertraline help with the recovery of AUD, in terms of behaviour, and grey matter brain volume changes.

Research Questions

Research Question 1: Is there a difference in self-reported relapse rates of alcohol addiction between participants taking an SSRI, and those not taking SSRIs?

Hypothesis: Participants taking SSRIs will have a lower relapse rate (thus higher recovery rate) of alcohol addiction, compared to participants not taking SSRIs.

Research question 2a: Are there differences in the volumes of specified areas of the brain between participants who have an alcohol addiction who take SSRIs, and participants who have an alcohol addiction and are not taking SSRIs (investigating the effect of the use of SSRIs in the context of alcohol addiction).

Hypothesis: There will be characterizable changes such as decreased grey matter brain volumes in the SSRI vs non-SSRI group.

Research question 2b: Is there a difference in volumes of specified areas of the brain between participants who are taking SSRIs and have an alcohol addiction, and participants who are taking SSRIs and have recovered from an alcohol addiction (investigating the effect of having an alcohol use disorder, in the context of taking SSRIs).

Hypothesis: There will be characterizable changes such as decreased grey matter brain volumes in the alcohol addiction compared to recovered group.

Exploratory Questions

Exploratory question 1: Is there a difference in relapse rates of alcohol addiction between those taking fluoxetine, citalopram, or sertraline?

We will conduct exploratory analyses into whether the use of one of either fluoxetine, citalopram, or sertraline are superior in increasing rates of recovery in alcohol addiction.

Exploratory Question 2a: Are there differences in the volumes of specific brain regions between participants who have taken either fluoxetine, citalopram, or sertraline who have recovered from an addiction to alcohol?

We will conduct exploratory analyses into whether the use of fluoxetine, citalopram, or sertraline have an increased difference in grey matter volumes of the brain in those who have recovered from addiction to alcohol.

Exploratory Question 2b: Are there differences in the volumes of specific brain regions between participants who have taken either fluoxetine, citalopram, or sertraline who have an ongoing addiction to alcohol?

We will conduct exploratory analyses into whether the use of fluoxetine, citalopram, or sertraline have an increased difference in grey matter volumes of the brain in those who have an ongoing addiction to alcohol.

Participants

All participants in this study will be selected as part of a subset of the UK Biobank. The UK Biobank aims to give researchers open access data from ~500,000 participants (~100,000 of whom will also have brain imaging data collected), across measures such as drug history, physical and physiological measures, and behavioural measures. Participants were selected form this online dataset based on specified inclusion criteria. All participants answered 'yes' to the question "have you ever been addicted to alcohol?", and had completed a T1-weighted structural MRI scan. The precalculated image derived phenotypes (IDPs) from volumes of specific brain areas from these participants will be then identified.

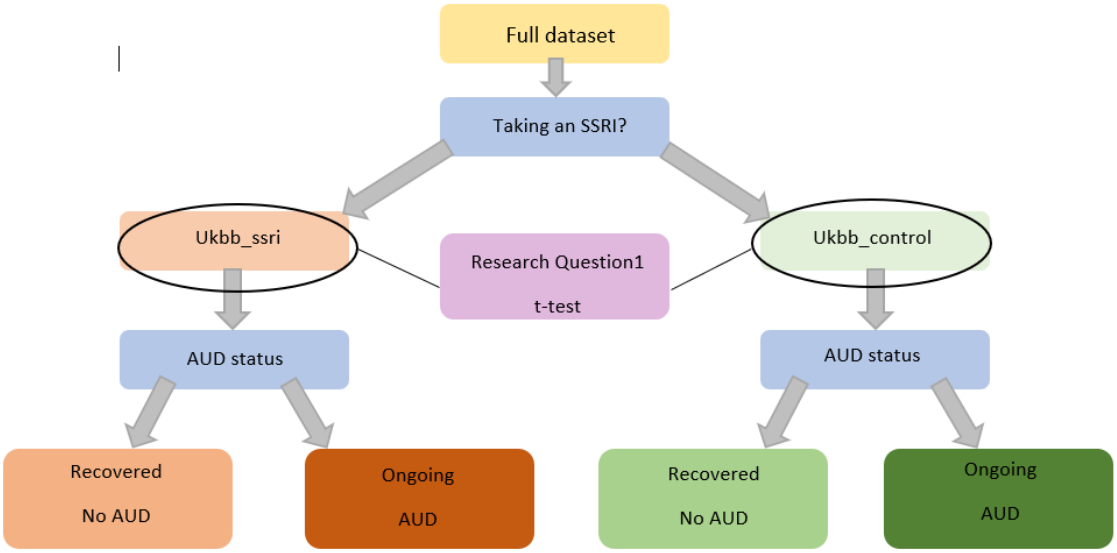
The SSRI group contains approximately 89 participants, all of whom have taken fluoxetine, paroxetine, sertraline, or citalopram at some point in their lives. They have also all answered 'yes' to the question 'have you ever been addicted to alcohol?' In this group, approximately 42 have taken citalopram, approximately 30 have taken fluoxetine, approximately 5 have taken paroxetine, and approximately 17 have taken sertraline. Overall, 5 participants have taken more than one medication.

The control group will consist of participants who have answered 'yes' to the question 'have you ever been addicted to alcohol', but do not take any of fluoxetine, citalopram, paroxetine, or sertraline. Eighty-nine participants who are matched in age, sex, and depression status will then be randomly selected from this group.

Analysis

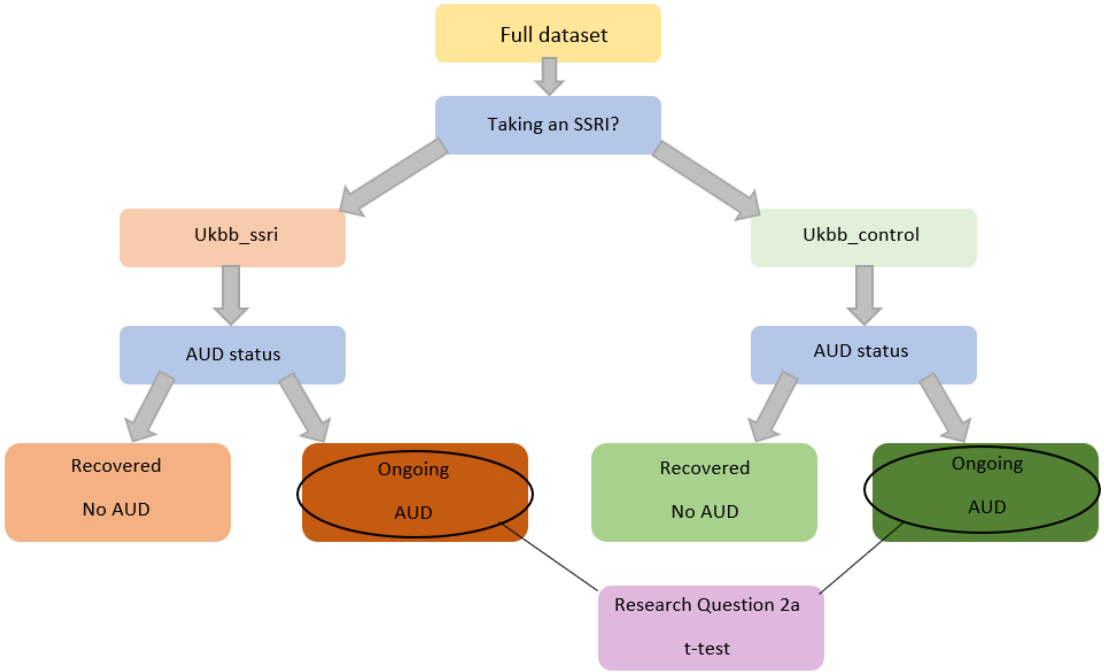
Research Question 1: Is there a difference in self-reported relapse rates of alcohol addiction between participants taking an SSRI, and those not taking SSRIs?

Participants will be grouped into those who take either fluoxetine, citalopram, sertraline, and paroxetine (ukbb_ssri group), or participants who do not take the aforementioned drugs (ukbb_control group). A two tailed unpaired t-test will be performed between these two groups with data from the column UID f.20415.0.0, asking "are you currently addicted to alcohol" yes/no. Yes will be coded as 1, and no will be coded as 0. Significance will be placed at $p<0.05$.



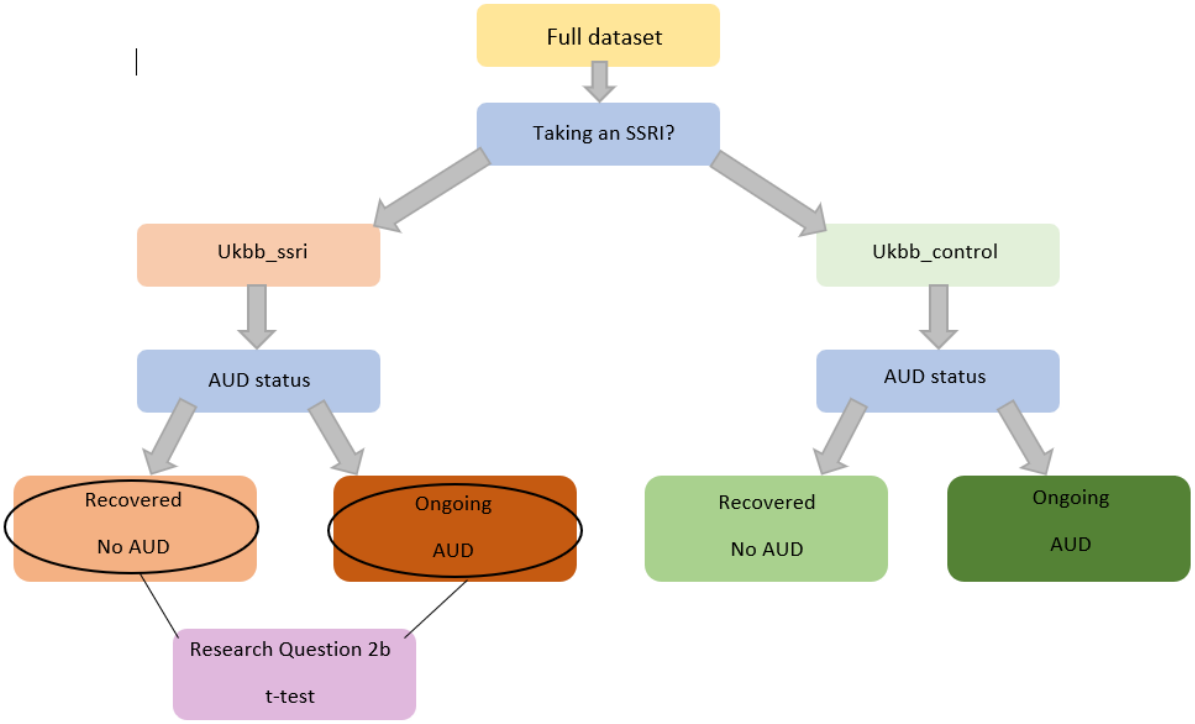
Research Question 2a: Is there a difference in volumes of specified areas of the brain between participants who have an alcohol use disorder who take SSRIs, and participants who have an alcohol use disorder and are not taking SSRIs (investigating the effect of the use of SSRIs in the context of alcohol use disorder).

All participants will have a current addiction to alcohol, indicated by answering 'yes' to the question 'do you have an ongoing addiction to alcohol?' Groups will be formed based on whether participants have taken fluoxetine, citalopram, paroxetine, or sertraline (left), or whether they have not had exposure to these drugs (right). A two tailed unpaired t-test will be performed between these two groups for each grey matter volume. These volumes have been pre-calculated and are stored as IDPs within the data. We will correct for multiple comparisons using false discovery rate (FDR) correction, to control for non-independent changes in grey matter volumes across the brain. The resultant significant p-value will be taken as $p<0.05$.



Research Question 2b: Is there a difference in volumes of specified areas of the brain between participants who are taking SSRIs and have an alcohol use disorder, and participants who are taking SSRIs and do not have an alcohol use disorder (investigating the effect of having an alcohol use disorder, in the context of taking SSRIs).

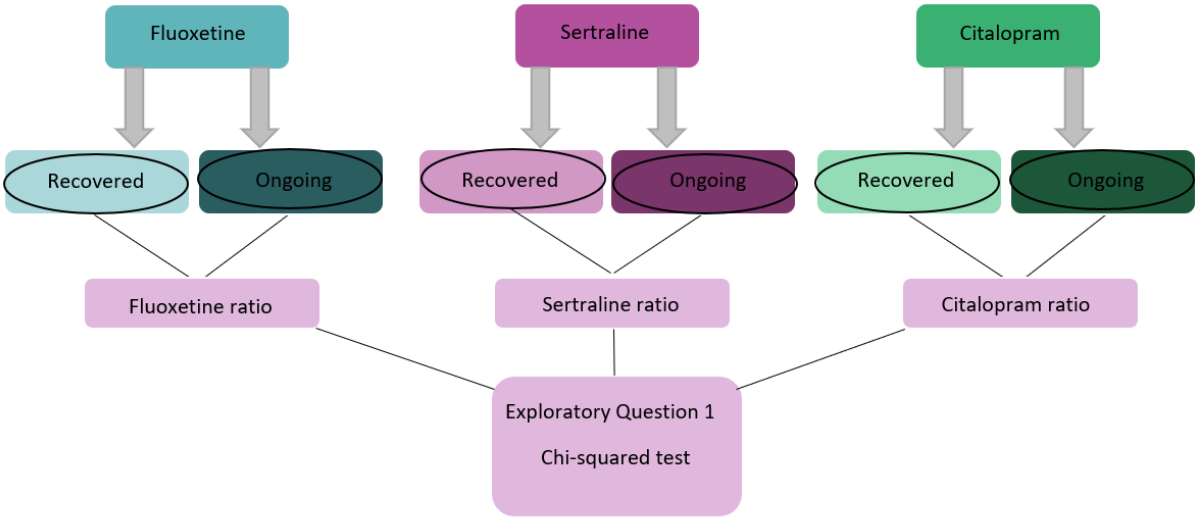
All participants will also have had exposure to fluoxetine, citalopram, fluoxetine, or sertraline. Participants will then be grouped based off whether they answered 'yes' or 'no' to the question 'do you have an ongoing addiction to alcohol?' A two tailed unpaired t-test will be performed between these two groups for each grey matter volume. These volumes have been pre-calculated and are stored as IDPs within the data. We will correct with FDR correction, to control for non-independent changes in grey matter volumes across the brain. The resultant significant p-value will be taken as $p<0.05$.



Exploratory Questions

Exploratory Question 1: Is there a difference in relapse rates of alcohol addiction between those taking fluoxetine, citalopram, or sertraline?

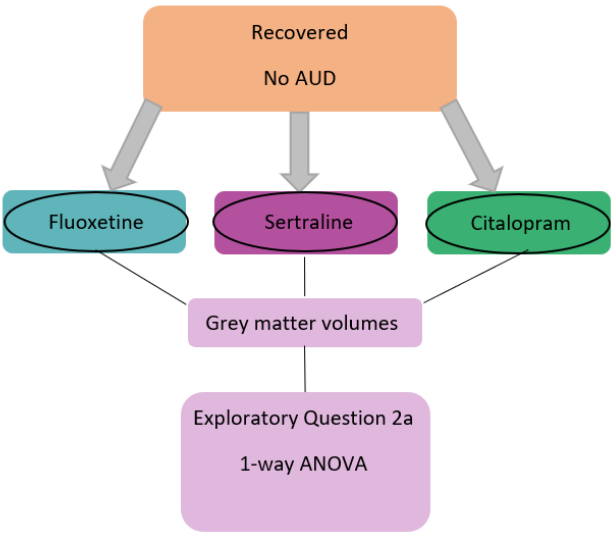
Participants will be grouped separately based on their exposure to three certain SSRIs, those being fluoxetine, sertraline, and citalopram. Paroxetine will not be included as this group contains five participants, and will be underpowered in any statistical analysis performed. A chi-squared test will be performed between groups using data from the column UID f.20415.0.0, asking "are you currently addicted to alcohol" yes/no. Yes will be coded as 1, and no will be coded as 0. Significance will be placed at $p<0.05$.



Exploratory Question 2a: Is there a difference in volumes of specific brain regions between participants who have taken either fluoxetine, citalopram, or sertraline who have recovered from an addiction to alcohol?

Participants will all have recovered from an alcohol addiction, and be split into three separate groups, depending on whether they have taken fluoxetine, sertraline, or citalopram (paroxetine will not be included for previously stated reasons). Differences between the three groups in grey matter volumes

of areas of the brain will be assessed using a 1-way ANOVA. We will correct for multiple comparisons using FDR correction, with a final significance placed at $p<0.05$.



Exploratory Question 2b: Is there a difference in volumes of specific brain regions between participants who have taken either fluoxetine, citalopram, or sertraline who have an ongoing addiction to alcohol?

All participants will have an ongoing alcohol addiction, and be split into three separate groups, depending on whether they have taken fluoxetine, sertraline, or citalopram (paroxetine will not be included for previously stated reasons). Differences between the three groups in grey matter volumes of areas of the brain will be assessed using a 1-way ANOVA. We will correct for multiple comparisons using FDR correction, with a final significance placed at $p<0.05$.

Version and revisions

This is version 1 of this analysis plan.

References

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