Understanding the neurobiological mechanisms of clozapine-induced Obsessive Compulsive Symptoms in schizophrenia and its treatment

Mental Health Research PhD Scholarship 2018: Dept of Psychology, Downing St, University of Cambridge

Supervisor: Professor Trevor Robbins

Lay Summary:

The use of Second Generation Antipsychotic drugs, particularly clozapine, has represented a considerable advance in treating schizophrenia, especially in otherwise treatment resistant patients. However, this drug is associated with negative consequences, including a distressing syndrome of obsessive-compulsive symptoms (OCS) which is little understood. Although the dopamine blocking drug aripiprazole appears to reduce clozapine-associated OCS, why this should work to counter the syndrome is not known. This drug may improve OCS by reducing the activity of a part of the frontal lobes of the brain called the anterior cingulate cortex which appears to be over-activated in OCD patients and is implicated in checking behaviour commonly observed in OCS. We plan to better characterise the underlying psychological and brain basis of clozapine-induced OCS and its remediation by aripiprazole. Our ultimate aim would be to provide a predictor or biomarker using EEG methods with behaviour of risk of OCS in early episode patients with schizophrenia to be treated with clozapine.

Student: Marjan Biria

Education: Bachelor of Clinical Psychology Vrije Universiteit Brussel (VUB), Brussel Belgium. Feb. 2009-Jun. 2013
Thesis: Effects of rumination and worry on working memory performance.

Master of Neuroscience.University of Geneva, Geneva Switzerland. Feb. 2014-Sep. 2015
Thesis: Investigating the EEG biomarkers of schizophrenia in a population with 22q11.2 Deletion syndrome.

Honours and Awards: Highest GPA of the class Master of Neuroscience, University of Geneva, Geneva Switzerland. Feb. 2014-Sep. 2015.First student with the maximum grade of 6 for Statistics and Probability course Feb. 2014-Sep. 2015
Master of Neuroscience, University of Geneva, Geneva Switzerland. Vahabzadeh Scholarship Sep. 2014-Sep. 2015

Research experience

Research assistant at FBM lab (10% teaching). University of Geneva, Switzerland. Nov.2015-Mar.2017
Intern at Functional Brain Mapping(FBM) lab University of Geneva, Switzerland. Jan.-Sep. 2015
Research: Conducting research about Visual processing in individuals with 22q11-Deletion Syndrome as a model for Schizophrenia.
Intern at Bavelier lab University of Geneva, Switzerland. July-Dec. 2014

Research: Conducting research about the positive and negative effects of video games on behaviour, attention and vision.

Intern at Geneva University Hospitals (HUG): EEG and Epilepsy Unit University of Geneva, Switzerland Feb.-June 2014

Research: Mapping of the language regions in epilepsy patients.

Faculty of Psychology, VUB, Belgium. 2012-2013

Research: Sleep study using polysomnography, preceded and followed by clinical and neuropsychological tests to examine cognitive functioning after a bad or good quality of sleep.

Faculty of Psychology, VUB, Belgium.2012-2013

Research: Cognitive and psychological scale interviews and providing clinical feedback.

Faculty of Psychology, VUB, Belgium. 2011-2012

Research: Performing different clinical and neurological battery tests and diagnosis.

Faculty of Psychology, VUB, Belgium. 2010-2011

Research: Using different Cognitive Assessment Batteries to evaluate the cognitive development in infants.

Teaching experience
Teaching EEG recording and data analysis. University of Geneva, Switzerland. 2015-2016
Statistics private lessons. Geneva, Switzerland. 2014-2015

Publication
Submitted for publication after a first round of revision: "Visual processing deficits in 22q11.2Deletion Syndrome "
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Start Date: September 2017

Study Aims:
Clozapine is one of the most effective second generation anti-psychotics (SGA) in the treatment of schizophrenia but is commonly associated with Obsessive Compulsive Symptoms (OCS), resulting in a negative prognosis [1]. However, the underlying neural and psychological basis of this syndrome and its possible treatment is not understood [2]. This project proposes a multimodal approach combining cognitive, EEG, magnetic resonance imaging and psychopharmacological methods to characterise this important syndrome, define its possible predictors/biomarkers, and test the possible mechanisms of its main treatment via the dopamine D2-receptor agent aripiprazole.

Final Report, 2022

I have submitted my thesis on 1st of May 2022 entitled "Neuropsychological and biological mechanisms of checking in OCD and clozapine induced Schizo-OCS " and passed my viva on 14th of July 2022. After submitting my thesis I have continued the data collection to reach our desired sample size. The data collection for all projects was finalised by June 2022 after about 1.5 year delay caused by the pandemic. The behavioural project has a final sample size of 30 healthy volunteers, 32 OCD patients, 21 schizophrenia patients with Obsessive Compulsive Symptoms (OCS), and 15 schizophrenia patients without OCS (both schizophrenia groups were treated with clozapine). I designed and developed a new checking paradigm to measure checking behaviour in an experimental setting, and in relation to clinical symptoms and cognitive deficits, as checking is the most common symptom in both schizo-OCS and OCD patients. Additionally, the two schizophrenia groups with and without OCS were compared against one another in order to characterise their clinical symptoms and cognitive profiles. I found dysfunctional checking only in schizo-OCS patients, which was captured for the first time in a laboratory setting. This checking behaviour was positively correlated with their clozapine dose and working memory performance. These findings are under preparation for publication and can shed light on the cognitive mechanisms underlying checking caused by clozapine.

In a second behavioural study, I adjusted the checking paradigm to capture dysfunctional checking in OCD patients as the previous task could only show this behaviour in the schizo-OCS group. Unfortunately, due to the feasibility issues caused by the pandemic and recruitment difficulties, schizophrenia patients could not be tested on this behavioural study and the 7T Magnetic Resonance Spectorscopy (MRS) study taking place on the same day. I managed to find the neurochemical correlates of excessive checking in OCD patients in a relevant region for OCD (Anterior Cingulate Cortex). Additionally, I found strong associations between neurochemical levels in another cortical region called Supplementary Motor Area and OCD symptom severity. The latter finding has relevant implications for treatment as the activity of this area can be modulated using a non-invasive procedure such as the Transcranial Magnetic Stimulation. There are 3 more publications under preparation disseminating these novel findings. I have reviewed and discussed the MRS findings in OCD patients in a book chapter for a volume on The Neurobiology and Treatment of OCD (2021), edited by Professors Robbins and Fineberg. To my knowledge and to this date, our study is the first 7T study in OCD and we believe the findings are publishable in a high impact journal.

I would like to express my immense gratitude to Mental Health Research UK for offering me a PhD scholarship, and for your generosity and trust to provide me additional funds to hire a research assistant to make up for the impact of the pandemic and to finish all studies in parallel.

Progress Report Year 4, 2021

The past year has been very challenging due to the pandemic's impact on our human projects. We did pause the projects during each lockdown and we did have many cancellations after the lockdowns. Despite all of these, we still managed to collect 26 MRS scans in 12 healthy volunteers and 14 OCD patients. With the help of our research assistant, who was hired with the funding you kindly provided, we also have collected behavioural data from 4 OCD patients, 2 healthy volunteers and 8 patients with schizophrenia.

During the first lockdown, I have written and published a book chapter reviewing the Magnetic Resonance spectroscopy and Positron (PET) findings in patients with OCD. This book chapter is also published as a journal article. The chapter is titled "Magnetic Resonance Spectroscopy (MRS) and Positron Emission Tomography (PET) Imaging in Obsessive-Compulsive Disorder" and is published in "Future Trends In Obsessive-Compulsive And Related Disorders Research".

We also have submitted another publication in schizophrenia patients titled "Clozapine-related obsessive-compulsive symptoms and their impact on wellbeing: a naturalistic longitudinal study". We found reduced wellbeing in schizophrenia patients experiencing OCD symptoms as a consequence of their treatment on clozapine and this was independent from their schizophrenia symptoms. This shows the negative impact of these symptoms on

patient's lives and the relevance of understanding more about them.
At the moment I am finalising a review paper on checking behaviour. This will be an important part of my thesis introduction and will be very helpful when interpreting the results of my checking paradigm briefly presented at MHRUK scholars' day. I am hoping to submit this review paper for publication in August.

I have also gathered all MRI scans collected in Cambridge in the past 10 years in OCD patients and healthy volunteers on the same scanner to perform machine learning and find the structural brain correlates of OCD symptoms. In addition, I have acquired an fMRI dataset using a probabilistic reversal learning task which looks at the way participants learn probabilistic reward contingencies associated with two responses, and how they will relearn them when the contingencies are reversed. I plan to perform computational modelling comparing the behavioural and brain correlates of potential cognitive deficits in OCD patients in comparison with healthy control participants.

Regarding my future plans, we will stop the behavioural data collection by the end of August and I will analyse the remaining behavioural data that were not presented during the scholars' day and write up the results both as a manuscript but also including them in my thesis.

As the pandemic caused a delay of at around 15 months in all our projects, together with my supervisor Professor Robbins we decided that it is better for me to extend my PhD until the end of April 2022. Hopefully this additional time would allow us to reach our initially planned sample size for the 7T MRS project and have more time to write a better thesis

Progress Report Year 3, 2020

During the third year of my PhD I have collected 27 MRS scans as part of a pilot study to optimise the parameters increasing the signal to noise ratio in our data, focusing on measuring GABA and Glutamate in relevant regions for both OCD and schizophrenia, such as the anterior cingulate cortex. Although this pilot study took longer than initially planned, we successfully detected these crucial parameters to implement in our experiments with OCD and schizophrenia patients (with and without OCD) and healthy volunteers. I also tested my new testing battery including my checking paradigm in 18 healthy volunteers, 10 OCD and 9 schizophrenia patients. The behavioural testing had to be put on pause as consequence of the Covid19.

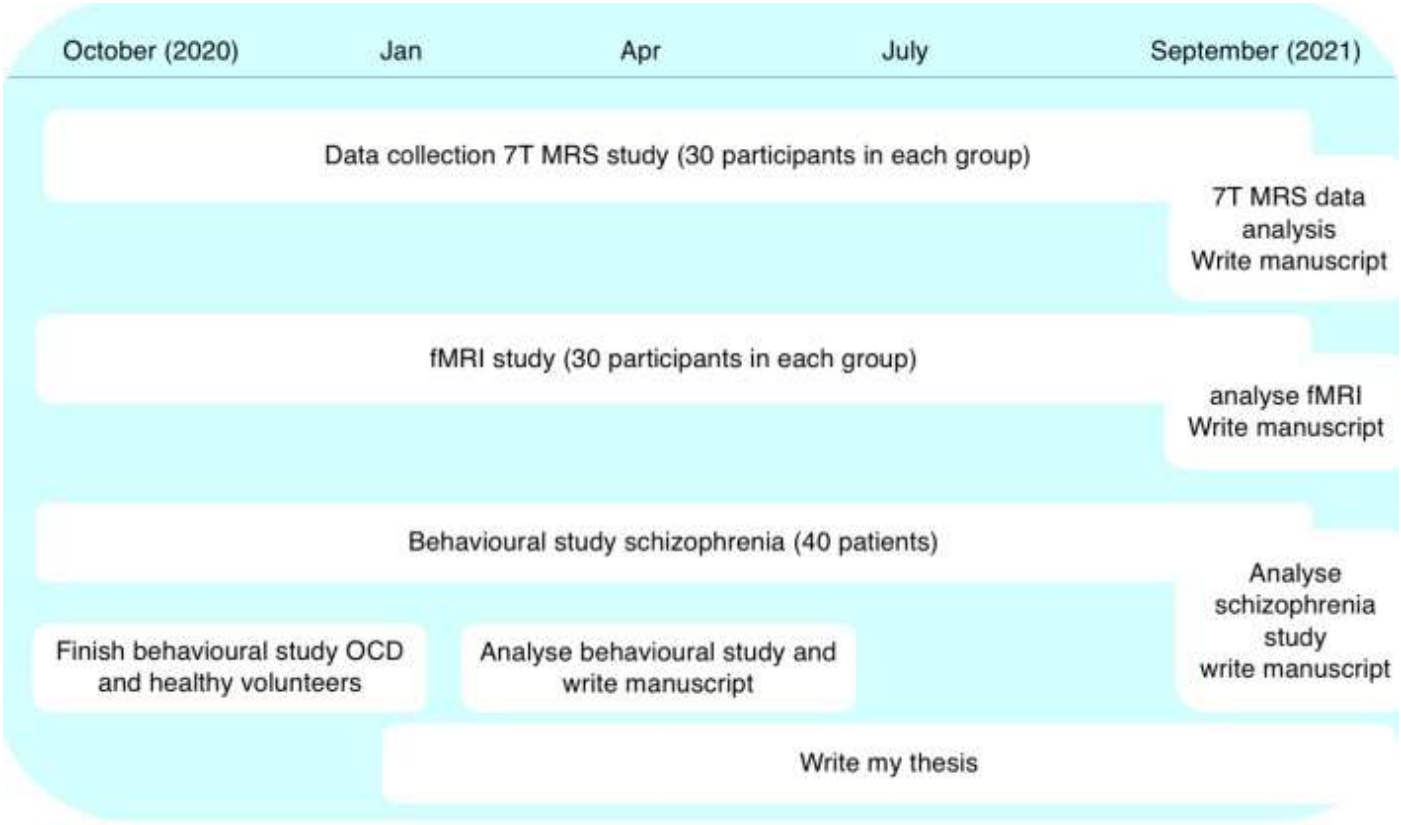
After performing the MRS pilot study, we realised the need to change some details and had to apply for two amendments for our schizophrenia and OCD ethics separately. The OCD amendment was approved but the reviewers asked us to apply for a whole new ethics application for the schizophrenia MRS study, which also took few months and is still under review (major delays as a consequence of Covid19). Additionally, I applied to another NHS ethics for a new fMRI study using a novel task to study habitual versus goal directed behaviour which is impaired in obsessive compulsive disorder and is predicted to highlight

functional changes in the anterior cingulate cortex, the main focus of our MRS imaging study. This ethics application was also approved. After our pilot study and the ethical approvals we were ready to start our experiments. In fact, I had screened participants including patients with OCD and schizophrenia and had booked them for testing. Unfortunately, just when everything was ready to start the final and main data collection of my PhD project, the Covid19 crisis started and I had to cancel all of my testing sessions. At the moment, all the studies are on hold and we predict we may possibly be able to resume our studies by October 2020. This means a delay of at least 6 months for our projects which for a last year PhD student is a substantial amount of time.

In the meantime, I have written a book chapter on magnetic resonance spectroscopy and PET findings in OCD patients. This chapter is part of a book titled “Future Trends In Obsessive-Compulsive And Related Disorders Research” edited by Professors Robbins and Fineberg. We have also decided to move some of our tests online so that we can keep testing participants during the lockdown. This will be part of a new study for which I applied for an ethics application to the Department of Psychology at Cambridge University, which is currently under review. I am also working on a review paper about checking behavior as one of the main symptoms of OCD. The review is currently under preparation for publication. I have just finished a 6 weeks online statistics course by University of Cambridge to expand my statistics knowledge. At the end of the course, I have scheduled online consultations with one of the teachers to make sure I have chosen best statistical tests to analyse the various datasets I have. Although I am analysing the data I have collected so far (written Matlab and R studio scripts from scratch), the sample is not sufficiently large enough for publication. I still need to test about 40 schizophrenia patients for both of my groups, as well as 5 OCD patients and 5 healthy volunteers.

The next academic year will be my last year and unfortunately it also means I have only a limited amount of time for data collection, analysis and writing up my manuscripts and thesis. Consequently, I may not have enough time to finish all the projects I had started, which is a shame, as I have found very interesting preliminary findings between pure OCD, schizophrenia with OCD, pure schizophrenia and healthy volunteers. I have been fortunate enough to have Prof. Robbins' Wellcome Trust funding supporting all these fascinating projects and I am aware that many people do not have this opportunity. However, at the moment due to the time I have lost as a consequence of the current crisis, I would not be able to finish these projects, unless I receive help from a part-time (e.g. 0.2FTE) research assistant to help me with the onerous task of behaviourally testing the patients with schizophrenia which would allow all behavioural and neuroimaging projects to run in parallel. Unfortunately, the Wellcome Trust grant does not cover the cost of hiring another research assistant and we need to find a different solution. Some funding bodies do provide a 6 months extension for their PhD students, however, I had planned to start a one year AI

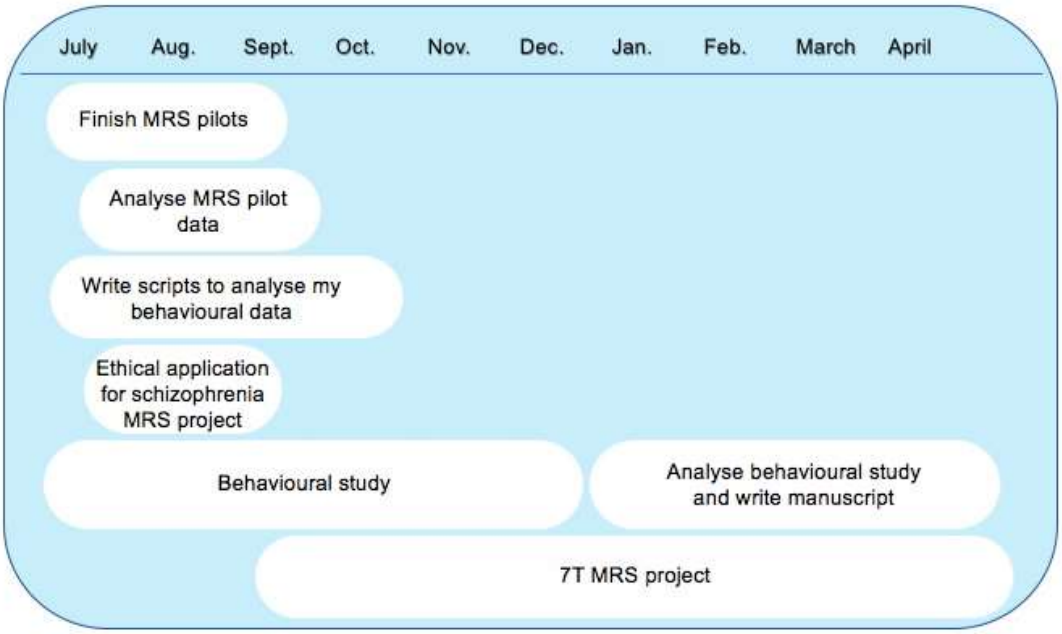
residency program from October 2021 and so would not benefit from such an extension. However receiving support from a research assistant would allow me to complete the projects without compromising my future plans. The difference would be between several unfinished projects and one or two papers with smaller sample sizes in lower impact journals, versus an investment of £6000-8000 (the yearly salary of a part time research assistant) allowing me to finish all the projects we started, and leading to several publications in high impact journals. The scheme below shows my next plan of action until September 2021, the end of my fourth PhD year:



Progress Report Year 2, 2019

During the second year of my PhD I have applied for two ethics applications to the Department of Psychology at Cambridge University and the NHS for our 7T Magnetic Resonance Spectroscopy (MRS) project to measure GABA and glutamate with a higher accuracy in healthy volunteers and patients with OCD and schizophrenia. The first application was for a pilot study in healthy volunteers to get us started with testing the different parameters. The second one was to test healthy volunteers and OCD patients for the actual study. Both these applications were approved. We still need to submit another separate ethical application for our schizophrenia patients which will be submitted this summer. I have written a first authored clinically oriented paper titled 'A cross sectional study of impact and clinical risk factors of antipsychotic-induced OCD'. This manuscript was accepted for publication by the European Neuropsychopharmacology journal in June and will be available for Open Access. To pilot my newly developed computer task (that measures checking behaviour and other different aspects of cognition), I tested 30 healthy

volunteers, 5 OCD and schizophrenia patients. I have then adapted my task according to the feedback I received and started the recruitment for my behavioural study testing my whole battery in both patients and healthy volunteers. So far, I have tested my whole behavioural battery (including this novel checking task) in 7 healthy volunteers, 11 patients with schizophrenia and 15 OCD patients. In parallel, I have also piloted 21 magnetic resonance spectroscopy scans in healthy volunteers in collaboration with the Wolfson Brain Imaging Centre. We plan to complete this pilot study in patients by the end of summer. Once we have analysed the spectroscopy data we will decide if any parameters need to be changed before we start our actual study. We hope to start our 7T MRS project in OCD volunteers in September followed by healthy volunteers. We plan to recruit schizophrenia patients in January after we finish the behavioural study. The picture below shows my next course of action until April 2020.



Progress Report Year 1, 2018

Understanding the neuropsychological mechanisms of clozapine-induced Obsessive Compulsive Symptoms in Schizophrenia

First Year PhD Report (summary) Candidate: Marjan Biria Degree: PhD Psychology

Funded by Mental Health Research UK Supervisor: Professor Trevor W. Robbins

Date: 07/07/2018

During the first year of my PhD I have applied for two NHS ethics applications to recruit schizophrenia, OCD, and healthy volunteers (separate applications for OCD and schizophrenia patients as they will be recruited from separate trusts). I have also obtained a research passport and two letters of access to recruit patients through the Cambridge and Petersborough Foundation Trust (CPFT, for schizophrenia patients) and the Hertfordshire

Partnership NHS Foundation Trust (HPFT, for OCD patients). The research passport and the letters of access allowed me to attend the clozapine and OCD clinics on a regular basis and be present during the patients' consultations with their consultant psychiatrists (Dr Emilio Fernandez and Dr Naomi Fineberg). This has been a great opportunity to spend time with patients outside the research context and understand their problems on a deeper and more personal level. I had also applied for NIHR CRN Portfolio for our study to be advertised in more trusts which was approved as well. This way the trusts that are working with OCD or schizophrenia patients and are interested in our research can contact us and help us with the recruitment. The whole process for all the applications mentioned above took about six months.

While waiting for the ethical approval and before being able to recruit participants, I have completed the following courses: How to Conduct Clinical Research Studies within CPFT, Graduate Core Skills Training, Good Governance, Deprivation of Liberty Safeguards (DoLS), Mental Capacity Act Module 1: Awareness for Researchers, Mental Capacity Act Module 2: Best Interests Decisions, MRI Safety course and Graduate Methods class. I have also analysed anonymised patients' data from the clozapine clinic registers about the association of patients' demographic information and their OCD symptoms induced by clozapine in collaboration with Dr Emilio Fernandez. I am now preparing the results for publication. I have also been helping with an ongoing project in our lab involving MRI scans, which besides being an educational experience for my MRS (Magnetic Resonance Spectroscopy) project, will make me a co-author of their publication.

I have developed a computerised task to look at the reactions of our patient groups to positive and negative feedback and whether they will show perseverative responding. I also have developed a second task to measure perseverative repetitions or stereotyped responding which we expect to see in our schizophrenia patients. I have written several Matlab script to extract the data for both tasks and to analyse their outputs.

I have been attending the 7T MRS meetings in University of Cambridge to inform myself more about the technique and build useful connections before we start our 7T MRS project. I was able to gather most people working with the new Siemens 7T MRS scanner (we will be working with) and created a group with whom we can have regular meetings to help each other with our knowledge and experience. At the same time, I am attending the 7T MRS sessions of an ongoing project to learn how to prepare and conduct our project later on this summer. I have examined my test batteries in a group of healthy and OCD volunteers. The healthy volunteers' findings are presented in the long version of my report, see below, while the OCD results are still being analysed.

First_year_report_MHRUK_MarjanBiria .pdf