Identifying clinical and cognitive endophenotypes for bipolar disorder: genetic risk score analysis of two large population cohorts

Bipolar Disorder PhD Scholarship 2015 - Cardiff University MRC Centre for Neuropsychiatric Genetics & Genomics

Supervisor: Dr Stanley Zammit, Dr Valentina Escott-Price,

Professor Daniel Smith

Summary:

Bipolar disorder is a relatively common but clinically complex disorder of mood and behaviour, characterized by episodes of depression and episodes of mania or hypomania. It has a major impact on individuals, their families and wider society. Although we know that most of the risk of developing bipolar disorder is genetically determined, we do not yet fully understand how genetic risk factors (of which over one hundred have been discovered in recent years) act together to bring about different manifestations of the disorder across the lifespan. This project will use a new approach, called genetic risk score analysis, to identify whether there are associations between high genetic loading for BD and more subtle clinical and cognitive features, such as abnormalities of sleep patterns, memory and attention problems, within two very large population cohorts. We expect that the main outcome of this work will be a greater understanding of how genetic risk for bipolar disorder is expressed during the life-course, with a view to identifying more robust clinical and cognitive markers for this condition and ultimately to improve the early identification of individuals at highest risk of developing bipolar disorder.

Research Student: Sumit Mistry

Hi everyone, I'm Sum and am very pleased to be starting my PhD this year at the MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University. I was very fortunate to be awarded the 4 year Bipolar Disorder Scholarship by Mental Health Research UK and this area is very close to my heart. I am supervised by Professor Stanley Zammit, Dr Valentina Escott-Price and Professor Daniel Smith, who is based in Glasgow University. My project aims to use a relatively novel approach, using polygenic risk scores to help understand how genetic risk for Bipolar Disorder manifests during the lifetime. I will be using the ALSPAC and Biobank UK cohorts and comparing to the Psychiatric Genetics Consortium BD dataset. I come from a Neuroscience background so I have a good grasp of the general ideas and concepts behind bipolar, but genetics is something very new to me! In that way, I am really looking forward to learning about

programming, statistics and being part of an expert team at the MRC Centre. I have no doubt that by the time I finish tis, I will be an excellent researcher with all the skills I need to succeed.

Start Date: September 2015

Scientific goal:

To gain a clearer understanding of how genetic risk for bipolar disorder is expressed during development, with the aim of identifying more robust clinical and cognitive endophenotypes for this condition and improve the early identification of individuals at high risk of developing bipolar disorder.

2018 Report

What is the project?

This project uses an approach called genetic risk score analysis, to identify whether there are associations between high genetic loading for BD and more subtle clinical and cognitive features, such as abnormalities of memory, attention problems and emotional and behavioural difficulties within two very large population cohorts. We expect that the main outcome of this work will be a greater understanding of how genetic risk for bipolar disorder is expressed during the life-course, with a view to identifying more robust clinical and cognitive markers for this condition and ultimately to improve the early identification of individuals at highest risk of developing bipolar disorder.

Update on proceedings

Over this past year I have been looking more closely into what genetic risk for BD looks like in childhood in a general population sample (ALSPAC). Following on from my first publication, I have written and submitted a paper titled: “Genetic risk for bipolar disorder is associated with childhood ADHD and features of hypomania in young adulthood” to the Bipolar Disorders Journal. As the title suggests, in individuals with a high genetic loading for BD, they are more likely to have ADHD, particularly the inattentive type as opposed to the hyperactive-impulsive type. Furthermore, we find that high genetic risk for BD is associated with being more likely to have hypomania in young adulthood. Further to these findings, I have been trying to identify whether specific aspects of cognition in childhood might be impaired in those who are at high genetic risk for BD, as in adults with BD, cognitive deficits are present through all phases of the illness (depressed, well and hypo/manic).

Future directions

The future directions for this project (over the final year of my PhD) will be to finish writing

my findings about genetic risk for BD and associations with cognitive measures in ALSPAC and complete my thesis. I also hope to investigate the relationship between high genetic risk for BD and measures of depression and anxiety in childhood.

2017 Report

Summary of aims

This project uses an approach called genetic risk score analysis, to identify whether there are associations between high genetic loading for BD and more subtle clinical and cognitive features, such as abnormalities of sleep patterns, memory and attention problems, within two very large population cohorts. We expect that the main outcome of this work will be a greater understanding of how genetic risk for bipolar disorder is expressed during the life-course, with a view to identifying more robust clinical and cognitive markers for this condition and ultimately to improve the early identification of individuals at highest risk of developing bipolar disorder.

Update on progress

During this past year, there have been a number of projects I have undertaken. Firstly, I have been focussed on submitting my previous analyses on whether different aspects of psychopathology during childhood are associated with an increased risk of hypomania in early adulthood. This is currently with the editor at the Journal of Affective Disorders awaiting a decision.

Following on from this, I have systematically reviewed the published literature to identify studies that have examined associations between polygenic risk scores for psychosis or affective disorder (showing an individual's genetic risk for these disorders) and a variety of outcome measures, to summarise how this literature has informed the causes of mood and psychotic disorders. This is now nearing completion with a view to submission by the end of June 2017.

Finally, I have been conducting genetic analyses to determine how the genetic risk for bipolar disorder and schizophrenia is manifest in the general population. Firstly, as a replication to another study the department have been analysing (the Christchurch sample from New Zealand), I examined whether the genetic risk for schizophrenia was elevated in individuals who were classed as being hypomanic. What we found was that the genetic risk for schizophrenia was higher in those individuals who were classed as being hypomanic, consistent with what the Christchurch sample data showed. Secondly, I have been using data from the Avon Longitudinal Study of Parents and Children (ALSPAC) to determine whether the genetic risk for bipolar disorder is elevated in individuals who had different aspects of psychopathology during childhood. These psychopathologies were the ones which we examined in the submitted paper and our preliminary findings suggest that the genetic risk for bipolar disorder is elevated in individuals being classed as hypomanic (when the degree of psychopathology is increasingly worse), having ADHD, having conduct

problems and peer relationship difficulties. Whilst I have not attended any further conferences this year, I have been to a number of courses to enhance my knowledge of regression modelling and use of a statistical software package.

Future directions

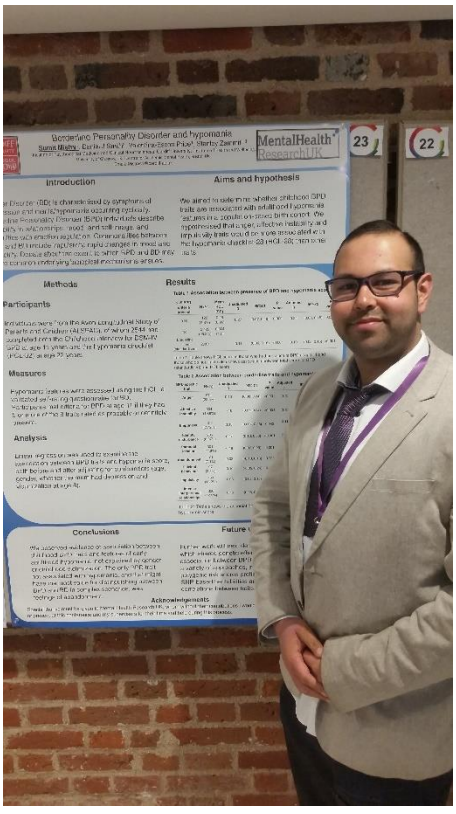
The future directions for this project (over the next year) will be to finish the systematic review, and continue to work on genetic analyses within ALSPAC to determine how the genetic risk for schizophrenia and bipolar disorder presents in childhood and adolescence, expanding the work I am currently doing on childhood psychopathology to include cognitive function and behavioural markers such as sleep duration during childhood.

2016 Report

What is the project?

This project uses an approach called genetic risk score analysis, to identify whether there are associations between high genetic loading for BD and more subtle clinical and cognitive features, such as abnormalities of sleep patterns, memory and attention problems, within two very large population cohorts. We expect that the main outcome of this work will be a greater understanding of how genetic risk for bipolar disorder is expressed during the life-course, with a view to identifying more robust clinical and cognitive markers for this condition and ultimately to improve the early identification of individuals at highest risk of developing bipolar disorder.

Update on proceedings



Over this past year I have been reading around the literature with a specific emphasis on grasping Bipolar Disorder, cognition (how we acquire and understand information) and about the aetiology (causes) of Bipolar. The main hypothesis we tested this year was “can borderline personality traits, ADHD and hyperactivity scores predict hypomania at age 22?” At this present time, I am writing this up as a paper with a view to be published. I have also been undertaking a systematic review on “the use of polygenic risk scores to inform our understanding of mood (depression and bipolar disorder) and psychotic disorders (schizophrenia and psychosis), though this is still in its infancy. I have been able to go to and present at a number of conferences both internally in Cardiff, and externally in Oxford (MHRUK conference), Cambridge (Wellcome Trust Genomics of Brain Disorders conference) and London Excel (Royal College of Psychiatrists international congress 2016).

Future directions

The future directions for this project (over the next year) will be to finish the systematic review, analyse sleep variables within ALSPAC (the longitudinal birth cohort I am working in) and whether sleep problems during adolescence can predict hypomania at age 22. I will also begin to derive my polygenic scores to test whether they are associated with my hypomania outcome in ALSPAC and any other phenotypes (such as the borderline personality disorder traits).