In Search of bio-psycho-social markers for the recurrence of adolescent depression.

Children and Young People's PhD Scholarship 2018 (2): Section of Clinical Psychology, School of Health in Social Science, University of Edinburgh.

Supervisor: Dr Stella Chan

Lay Summary:

Half of depression cases emerge in youth. Adolescent depression is notoriously difficult to treat and highly recurrent. Once an individual has had one episode of illness, the chance of developing a second episode is 60%; after two and three episodes, the chances rise up to 70% and 90% respectively. We urgently need to develop more effective treatments on the early stage of illness, before it develops into a recurrent pattern. This PhD will therefore focus on young people who have recovered from depression. The key hypothesis is that the experience of depression may result in biological and psychosocial changes ('scar effects') that make the individual more at risk for developing future episodes of illness. This PhD will examine these features, focusing on three areas:

i. Emotional processing – the way we attend to, interpret, and remember emotional information;

ii. Reactivity to stress – both in terms of biological functions indicated by cortisol levels (the 'stress hormone'), quality of sleep, and psychological strategies of emotional regulation;

iii. Psychological scar effects – the way individuals cope with the sense of shame and stigma that are often associated with mental health difficulties.

This project consists of three studies using both quantitative and qualitative methods with longitudinal follow-up assessments to examine short- and long-term outcomes. Qualitative interviews will help capturing the lived experience of adolescent depression and identify factors that are subjectively important. The ultimate goal is to inform the development of better treatment and preventative strategies that can transform the quality of life across the life span.

Research Student: Niamh MacSweeney

Hello! My name is Niamh and I am due to start my PhD in Clinical Psychology at the University of Edinburgh in January 2019.

I have just completed a joint-honours degree in Psychology with English Literature at Trinity College Dublin, where I graduated with first-class honours. My final year dissertation leveraged a novel behavioural assay of coping and investigated its relationship with depressive symptom severity in female adolescents. For the past year, I have been working as a part-time research assistant at the Trinity College Institute of Neuroscience on a Brain and Behaviour Research Foundation funded project investigating the neural correlates of coping and emotion regulation in adolescent depression.

Throughout my undergraduate studies, my research pursuits have become increasingly focused on youth mental health and I am very excited to be pursuing a PhD in this field. Outside of research, I volunteer on a

weekly basis with ISPCC Childline. I look forward to working with Dr Stella Chan and colleagues in Edinburgh and would like to thank Mental Health Research UK for this great opportunity.

Start Date: September 2018

Scientific Goal:

Half of depression cases emerge by the age of 25 [1]. Adolescent depression is typically a more severe form of the disorder and is notoriously difficult to treat [2, 3]. Notably, risk for recurrence increases with each episode of illness. Following one episode, 60% suffer another episode; after two and three episodes, the probabilities rise to 70% and 90% respectively [4, 5]. Hence, the experience of depression may itself have a causative influence on further clinical outcome. The overarching hypothesis is that 'scar effects' from previous depressive episode(s) contribute to further vulnerability. The scientific goal of this proposed PhD is to identify these scar effects by examining which features follow a first depressive episode in adolescent individuals and which act as vulnerability markers predicting future recurrence of illness.

Based on a developmental perspective, this PhD will target the period immediately following the first depressive episode in adolescence, to examine the dynamic change of risk and resilience mechanisms over this critical time. This is built upon our two current Wellcome Trust funded studies (led by the applicant) examining how biological and psychosocial risk mechanisms emerge in adolescence prior to illness onset. Together, our findings will make a significant scientific contribution regarding the mechanisms that underpin the occurrence and recurrence of adolescent depression, a question that has been identified by patients, carers, and mental health professionals as the top priority of depression research [6].We will also take an interdisciplinary approach, examining across biological, neural-cognitive and psychosocial mechanisms. This holistic approach, supported by an interdisciplinary supervision team situated in the unique multidisciplinary environment at the University of Edinburgh, is important in bridging the gaps in knowledge due to traditional unhelpful disciplinary divides. This study will have an impact on the development of better treatments that can build long term resilience against recurrence of illness, improving quality of life from a young age.

Progress Report Year 4, 2022

It is hard to believe that I am penning my last annual review for MHRUK! Time has flown over the course of my PhD, and this past year was no different.

From September to November 2021, my work focused on my second PhD project, entitled: "The role of brain structure in the association between pubertal timing and depression risk in an early adolescent sample (the ABCD Study®): A registered report. This project uses pre-existing data from the Adolescent Brain and Cognitive Development (ABCD) Study, a US-based study involving nearly 12,000 young people. This study hypothesises that earlier pubertal timing will be associated with later depression, and that this relationship will be related to differences in brain structure in areas related to emotion regulation and cognitive control. This paper is currently under a second round of review and will hopefully be accepted for publication soon. I presented a poster on this study at the Organisation for Human Brain Mapping (OHBM) international conference in Glasgow in June 2022. Attending an in-person conference was such a welcomed change after Covid and it was great to chat to researchers from all corners of the globe about my work!

Since January 2022, I have also been working on analysing the neuroimaging data that I collected in 2020-2021. The aim of this study was to investigate the neural basis of irritability in adolescent depression. We worked with young people to design a novel task targeting irritability, whereby young people were asked to imagine being in irritating scenarios as vividly as possible when in an MRI scanner. We can then examine what brain regions are active during this task, and whether this differs between young people with increased depressive symptoms or irritable mood. Data analysis for this project is still ongoing. However, I will be presenting some of our findings at the

Flux Congress in Paris this September. We found that the anterior cingulate cortex, an key emotion regulation region of the brain, was part of a more fragmented brain network in individuals with higher levels of irritable mood. Many thanks to MHRUK for supporting my attendance to this conference. I look forward to reporting back about the experience. As part of this project, I also worked with youth researchers to write a narrative literature review on the neurobiology of irritability in adolescent depression, which is currently under review. A pre-print of our paper is available **here.**

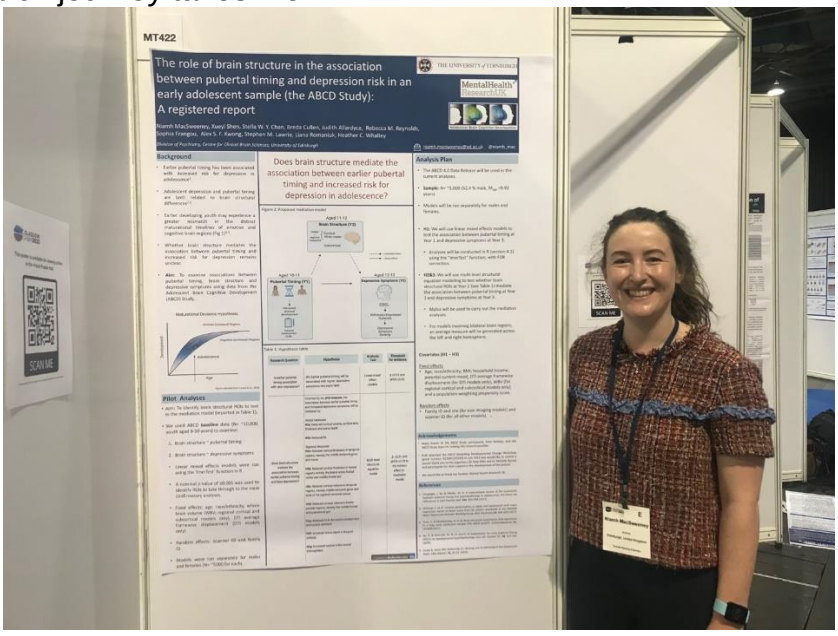
Another ABCD project I led with a post-doc in our group, Dr Xueyi Shen was published in EClinicalMedicine as an open-access article (full paper available **here**) in December 2021 We found that alterations in brain structure (e.g., cortical and white-matter microstructure) were associated with depression in early adolescence, and that these depression-related brain features are also found in adult depression. However, we also found some differences in brain structure, such as surface area, that have not been demonstrated in adult depression samples, and thus, may represent an adolescent specific vulnerability.

Following the ABCD workshop I attended last year, I was joint-first author on a paper entitled: A practical guide for researchers and reviewers using the ABCD Study and other large longitudinal datasets, which was published in Developmental Cognitive Neuroscience in June 2022 (full paper available **here**).

A highlight over the past year was an invited research visit to Professor Christian Tamnes' group at the Department of Psychology, University of Oslo in November 2021. I was awarded a Guarantors of Brain travel grant for the value of £600 to fund this trip. During the trip, I presented my PhD work to date to Prof. Tamnes' group and the broader research centre. I also attended a number of seminars and had meetings with the Tamnes group to learn more about their research on adolescent brain development and mental health outcomes. We had many fruitful and engaging discussions and I thoroughly enjoyed my time in Oslo.

In April 2022, I was awarded "Highly Commended" in the British Neuroscience Association Student Credibility Prizes for my commitment to open research practices. I was also the co-organiser of the Edinburgh Open Research Conference in May 2022 at which I delivered a workshop on Registered Reports.

I'm currently in the midst of writing my PhD thesis, which I will submit later this autumn. Many thanks again to MHRUK for funding my research and I look forward to seeing where the next chapter of my research journey takes me.



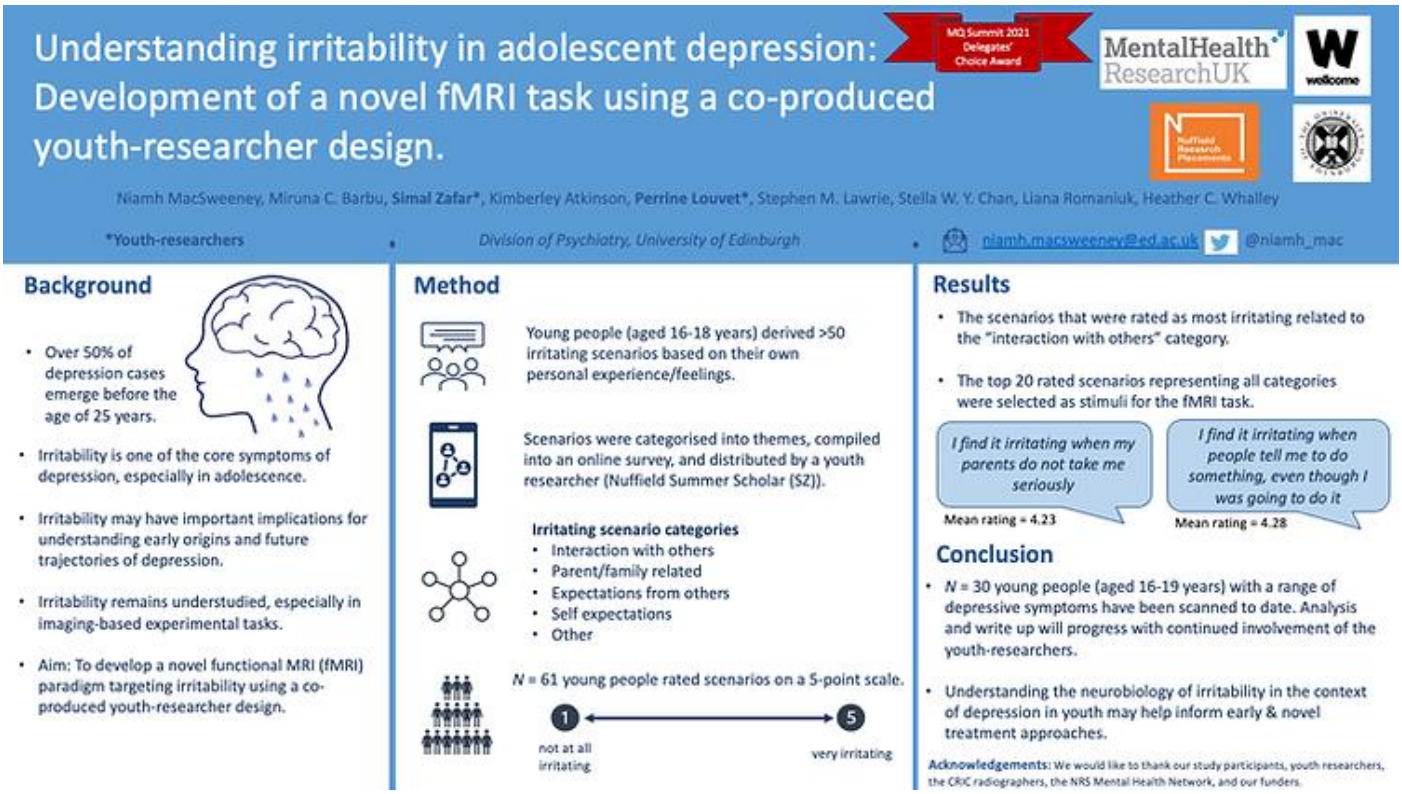
Presenting my poster at OHBM 2022, Glasgow, June 2022.

Progress Report Year 3, 2021

Over the past year, my work has focused on two main projects, data collection for a neuroimaging study and another data analysis-based project looking at pubertal development, brain structure, and depression risk.

Thankfully, the halt to face-to-face data collection due to Covid-19 ended in October 2020 and I was able to resume data collection that November. The aim of this neuroimaging project is to better understand how certain thinking styles and behaviours, such as reward processing and irritability, are associated with brain structure and function in adolescents with depression. To examine these cognitive processes, we used some existing functional MRI (fMRI) tasks from our research group as well as designing a novel fMRI task targeting irritability. My favourite aspect of this project was the fact it was co-produced with young people. This means that young people have been, and will continue to be, involved in every stage of the research project from the development of our research questions and tools to the dissemination of our results. We had the opportunity to present this work at the MQ Mental Health Science Summit in May 2021 and were delighted to be awarded the Delegates' Choice Poster Award. You can see our poster **here**.
We wrapped up data collection for this project in June 2020 and although recruitment was more challenging due to Covid, we successfully recruited and scanned over 30 young people, aged 16-19 years. I am looking forward to analysing the data over the coming months and preparing a manuscript for publication. Alongside the data collection, I have also been working on a literature review on the neurobiology of irritability in adolescent depression, which I will prepare for publication this autumn.

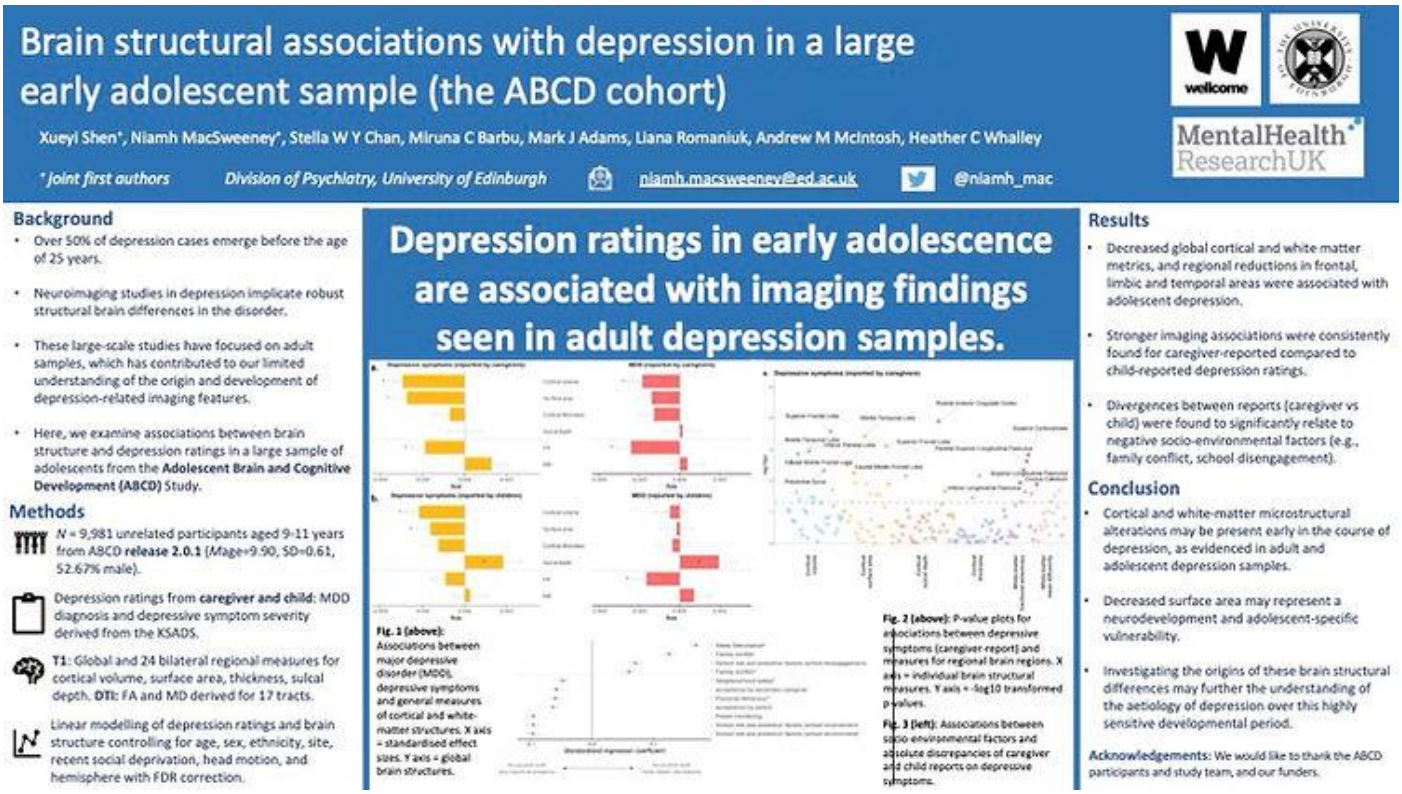
My data analysis-based project uses data from the Adolescent Brain and Cognitive Development (ABCD) Study. This longitudinal study includes behavioural, biological, and socio-environmental data from nearly 12,000 young people across the US.



I am currently using the baseline data (young people aged 9-11 years) to examine the role of neurobiology in the association between pubertal timing (i.e., pubertal development relative to same-age peers) and depression in early adolescence. This project will take the form of a Registered Report, an Open Research publishing format that promotes transparent methods and

data analysis plans, which aims to tackle the current bias towards “significant” findings in a lot of research. I was fortunate to be selected to attend the ABCD Longitudinal Modelling summer school in July 2021. This 5-week long course greatly helped the development of this project and also afforded me the opportunity to meet other researchers from across the globe working with the dataset. The summer school has been a highlight of my PhD to date and I look forward to putting the knowledge gained into practice and sustaining collaborations over the remainder of my PhD and beyond! I will be presenting a poster for this project at the Flux 2021 virtual conference this September and plan to submit stage 1 of the registered report in the next few weeks.

Another ABCD project I led with a post-doc in our group, Dr. Xueyi Shen, is currently under review (preprint available **here**). This project examined brain structural associations with depression in early adolescence. We found that alterations in brain structure (e.g., cortical and white-matter microstructure) were associated with depression in early adolescence, and that these depression-related brain features are also found in adult depression. However, we also found some differences in brain structure, such as surface area, that have not been demonstrated in adult depression samples, and thus, may represent an adolescent specific vulnerability. We presented this work at the Organisation for Human Brain Mapping (OHBM) conference in June 2020 and you can see our poster **here.**



Outside of my PhD work over the past year, I co-founded the Edinburgh branch of **ReproducbiliTea,** an open-science grassroots journal club initiative, in September 2020. This is a university-wide, monthly journal club where we meet to discuss ideas and issues about improving research (integrity), reproducibility, and the broader open research movement. All of our sessions are recorded and available on our **YouTube Channel**. I have also taken part in a number of public engagement and science communication activities, including a digital story telling workshop about my PhD research. You can view my digital story, entitled, The Whirlwind of Adolescent Depression **here**, which was part of Edinburgh Science Festival 2021.
I was also selected as the University of Edinburgh representative to attend the **LERU Doctoral Summer School**, which will be held virtually from August 9th-13th 2021. Hosted by Trinity College Dublin, the summer school will focus on the role, value, and influence of the “Expert” in research and in society.

I look forward to continuing to work on my ABCD projects and will undertake some follow-on projects over the coming year. Further, I am excited to start the data analysis of the fMRI data and start writing up results over the coming months. It's hard to believe I am approaching the final furlong of my PhD journey but I'm eager to move forward with my studies and pull everything together into a thesis by December 2022!

Progress Report Year 2, 2020

I write this year's progress report under the most unusual circumstances — Covid-19 lockdown. Whilst drafting continency plans and risk assessments for my PhD study, a complete halt to face-to-face data collection due to the outbreak of a global pandemic was something none of us had anticipated. As a result, the shape of my PhD has altered significantly. While there were some stresses along to way as I grappled with the changed research and working environment, thankfully, I was able to adapt my PhD and research methods to suit the Covid-19 restrictions.

As mentioned, the outbreak of Covid-19 prevented any data collection from going ahead. Frustratingly, the bulk of my work over the past year has focused on preparing for data collection, which was originally planned to comprise the majority of my PhD workload. Although we had initially planned to begin data collection in September 2019, we were advised to obtain NHS ethics approval for the study which delayed our start date for recruitment by a few months. Even though this process was lengthy, I feel that it strengthened the study protocol and also provided me with invaluable research experience, mostly notably, attending an NHS Research Ethics Committee meeting. Alongside the ethics application, my work through the winter months of 2019 focused on preparing the materials for data collection, such as the programming and piloting of computerised cognitive tasks, training and piloting the clinical interview, as well as completing courses in R programming for data analysis. I also co-authored a literature review on cognitive maturity in adolescents for the Scottish Sentencing Council, which was published earlier this year. When my NHS ethics approval came through in February 2020, I was ready to hit the ground running with recruitment and data collection — unfortunately, this work suddenly came to halt in mid-March with the outbreak of Covid-19 in the UK.

When reality catches up with the plan, it is best to change the plan, and that is precisely what I did. After consultation with my PhD supervisors and MHRUK, we decided to switch to a data analysis-based PhD. Thankfully, our research group has access to some excellent pre-existing datasets, two of which I can use to answer my original research questions, without much alteration. I will be leveraging the Avon Longitudinal Study of Parents and Children (ALSPAC) Study, which is based in the UK, as well as the Adolescent Brain and Cognitive Development (ABCD) Study in the US. Working with "big-data" will be a new challenge for me but I am confident that it will foster the development of strong data analysis skills, which I will be able to apply to future projects. It is still unknown when or if data collection will be able to resume but, in the meantime, I am happy that I am still able to answer the research questions at the heart of my PhD. I swapped a summer of face-to face- data collection with young people in Edinburgh for one in rural Ireland with my laptop, nature, and my family for company!

Since the start of lockdown, I have assisted on a project examining the brain features associated with adolescent depression using the ABCD study data. This work has been a helpful introduction to working with big data and has prepared me for leading my own data projects for my PhD research — I'm looking forward to continuing this work for the rest of the year. Outside of my PhD work, I have had the opportunity to co-supervise a high school student this summer as part of the Nuffield Research Placement programme. I'm glad that this project was still able to take place virtually as summer schools, conferences, and seminars I had planned to attend this year have unfortunately been cancelled. The Royal Society STEM Partnership grant that I was awarded with a local high school has also been suspended. We were all very lucky to attend the MHRUK Scholars' Day in Cardiff in early March. It was great to catch up with the MHRUK team and hear about all the exciting research they are funding. I look forward to seeing everyone again next year,

when hopefully life will have returned to some kind of normality. In the meantime, I'm grateful that I've been able to adapt my PhD and continue my research in these strange times!

Progress Report Year 1, 2019

Since beginning my doctoral studies in January 2019, I have had a busy couple of months to say the least! I spent the first few weeks settling into life in Edinburgh and was really impressed by the level of support offered by the university for new PhD students, from a comprehensive induction week to an array of research training courses. This made the adjustment from undergraduate to postgraduate study that bit smoother. I enrolled on a variety of courses on research methods and training, which was a great aid when writing my literature review — the focus of my PhD work for the first couple of months. This review helped shape and finalise my PhD protocol, which I submitted as my 10-week review, a requisite for all first-year doctoral students at the University of Edinburgh. While this required a significant amount of time and effort, I found the exercise to be incredibly helpful as it clarified my research questions and laid out a clear plan for the project going forward.

Moreover, this review laid a strong foundation upon which to start my ethics application. "Ethics" is a term that often strikes fear into the hearts of many PhD students and researchers, and although I was initially daunted by the prospect of completing this lengthy application, it was thankfully easier than I anticipated. Due to the fact that I will be working with a vulnerable population (young people with depression) during my PhD, it was necessary to submit the highest level of ethics clearance, which involved a lot of contingency and safeguarding plans! Thankfully, I am putting the final touches to the application and I am due to submit it to the Ethics Committee by the end of July 2019. Following ethics approval, I will begin recruitment and data collection in September 2019, which will keep me busy for the next few months… or years! Given that my project involves a follow-up at various time points over a two-year period, there is some pressure to start data collection as soon as possible but thankfully, our timeline is on target so far.

Outside of my PhD project, I have immersed myself in the University's vibrant public engagement scene. Over the (gloriously sunny!) Easter weekend, I participated in this year's Edinburgh Science Festival with Edinburgh Neuroscience at the National Museum. I spent the weekend chatting to families about the wonderful world of brain research, which involved dissecting lamb brains in a rather hot seminar room! Further to this activity, in June another PhD student and I were awarded a Royal Society STEM Partnership Grant to the value of £3000. This funding will allow us to undertake a year-long STEM project entitled, "Does our biology influence our mood?", in partnership with Musselburgh Grammar school. The project will provide a better understanding of psychiatric genetic research through a series of practical workshops as well as a student-led research project. The project will run during the 2019-20 school year, so I will certainly be kept busy for the next while.

Although only in the first year of my PhD, I managed to find myself in the university final of the 3-Minute Thesis competition, which was held at the end of June. I took part in the School heat back in April for fun as they were looking for more sign-ups so to have made it all the way to the final was a real bonus! Explaining one's research in a comprehensive, yet engaging, manner to a lay-audience in three minutes is no easy task. However, I feel that my science communication skills have greatly developed from the experience and I would really encourage all PhD students to enter if the opportunity presents itself.

You can check out a video of my presentation
here: **https://www.youtube.com/watch?v=gnlJ1gT-UeA**

Between data collection and public engagement activities, I have a busy year ahead but a full-plate is a happy plate, right? Thanks to MHRUK again for enabling all these research activities. I look forward to seeing the team at our next Scholars' Day.