BRAIN CONNECTIVITY AND FAMILIAL RISK FOR MAJOR MOOD DISORDERS

by

Daniel (Murage) Murage

Submitted in partial fulfilment of the requirements for the degree of Master of Science in Medical Neuroscience

at

Dalhousie University
Halifax, Nova Scotia
June 2023

Dedication

To my parents, who have always believed in me, supported me, and allowed me to come survive these cold Canadian winters. Not a day goes by without thinking of you, missing you. To grandma and grandpa, whose wise and loving words remain with me and bring a smile to my face everyday; I only wish you were around to hear all about it. And to the people of Gitero: I think of our promise everyday, and it will be so wonderful to see your friendly and welcoming smiles soon. I am bringing the degree home, and we will have a party!

Table of Contents

List of Tables

List of Figures

Abstract

Mood disorders are associated with differential connectivity in the default mode network (DMN). It is not clear whether these differing DMN connectivity precedes illness onset. We investigated DMN connectivity in 126 offspring of parents with major mood disorders and 78 control offspring of unaffected parents (ages 9 to19), and also studied how connectivity is associated with depression symptoms. There were no differences in DMN connectivity of those at high familial risk compared to controls, and no significant relationship between DMN connectivity and depression symptoms. Following this, we studied the association of DMN and salience network (SN) connectivity with mood disorder onsets so as to find subject specific variables that can complement family history and aid in better identification of those at risk. Our analysis revealed that connectivity within and between the DMN and SN was not associated with mood disorder onsets, but depression symptoms were. Therefore, connectivity might not complement family history in better identification of those at risk of developing mood disorders, but clinical risk can.

List of Abbreviations Used

AI	Anterior insula
BD	Bipolar disorder
BOLD	Blood Oxygen Level Dependent
CI	Confidence interval
CSF	Cerebrospinal fluid
dACC	Dorsal anterior cingulate cortex
DMN	Default mode network
dMPFC	Dorsal medial prefrontal cortex
DSM-5	Diagnostic and Statistical Manual – Fifth Edition
DMN-to-SN	Default mode network to salience network
EPI	Echo-planar imaging
FD	Framewise displacement
FHR	Familial high risk
fMRI	Functional Magnetic Resonance Imaging
FORBOW	Families Overcoming Risk and Building Opportunities for Wellbeing
FSIQ	Full Scale Intelligence Quotient
ICC	Intra-class correlation
IQ	Intelligence Quotient
K-SADS-PL	Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version
MDD	Major depressive disorder
MRI	Magnetic Resonance Imaging
PCC	Posterior cingulate cortex
ROI	Region of interest
SCID	Structured Clinical Interview for DSM-5 Disorders
SN	Salience Network
TR	Repetition time
WM	White matter
YETI	Youth Experience Tracker Instrument

Acknowledgements

I'd like to thank several people, whose support and guidance made the completion of this thesis possible. Firstly, my supervisor Rudolf, as well as my thesis committee – Chris, Aaron, Kazue –, whose guidance, mentorship and feedback has been invaluable. Secondly, Vlad and Carl, who taught me the programming skills needed to analyse neuroimaging data. And Anna, for your thoughtful feedback and support through the stressful times. Thirdly, I'm very grateful to Sara and Lucy, your friendships brightened my days during the cold winter. And lastly, a big shout out to the FORBOW team members and families for their dedication to the study. Asanteni sana!

CHAPTER 1: INTRODUCTION

Brain Connectivity and Familial Risk for Major Mood Disorders

Mood disorders, which include depression and bipolar disorder, begin in late adolescence to early adulthood, often affecting individuals over their lifetime (Herrman et al., 2022; Rakofsky & Rapaport, 2018). They present early, with subthreshold symptoms, and they have been associated with differential connectivity in the default mode network (DMN) (Pine & Fox, 2015; Price & Drevets, 2012). However, there is no consensus on whether differing DMN connectivity is associated with familial risk for mood disorders. Therefore, we investigated DMN connectivity in youth at high familial risk for mood disorders, and the association between this connectivity and depression symptoms. Our results showed that mean DMN connectivity for the familial high risk group is similar to that of controls. Additionally, DMN connectivity was not significantly associated with depression symptoms. These results indicate that DMN connectivity might not be a neural indicator associated with familial risk for major mood disorders.

Following up on the first project, we decided to investigate whether connectivity in the DMN and SN is associated with mood disorder onsets. Given that family history, which is a strong risk factor associated with mood disorders, is not always reliable, we hypothesized that connectivity might complement family history and help in better prediction of those at risk of developing mood disorders (Clark et al., 2022). Our results revealed that connectivity was not associated with mood disorder onsets, although depression symptoms were. This implies that depression symptoms can complement family history and aid in better prediction of mood disorder onsets, while connectivity might not.

CHAPTER 2: BRAIN DEFAULT MODE NETWORK CONNECTIVITY AND FAMILIAL RISK FOR MAJOR MOOD DISORDERS

Abstract

The default mode network (DMN) is a network that shows increased connectivity during rest, and is thought to underlie self-referential thought processes. Connectivity in the DMN has been implicated in major mood disorders. Previous studies have reported either increased or no differences in the DMN connectivity of youth at high familial risk for mood disorders, and that d symptoms precede the onset of major mood disorders. The purpose of the current study was to investigate DMN connectivity in a sample of youth at high familial risk of developing major mood disorders, and characterize the correlation between DMN connectivity and d symptoms. Our sample of 204 participants (Familial High Risk (FHR): 126, Mean age=13.42, SD=2.91; Controls: 78, Mean age=13.22, SD=2.65) filled a depression questionnaire prior to going into the scanner. Linear mixed model analysis found no differences in DMN connectivity between the FHR and Control groups (B= -0.01, SE = 0.02, $p > 0.05$), and a non-significant correlation between DMN connectivity and depression symptoms (FHR: $r = 0.06$, $p > 0.05$; Controls: $r = -0.18$, $p > 0.005$). The calculated power for this study showed that we needed 198 participants to get an effect size of 0.4, so our sample size is sufficient to find reliable results. Our results indicate that DMN connectivity might not be a risk factor associated with familial risk for major mood disorders. Future research using advanced techniques – such as brain age gap – and a longitudinal design is needed to validate these results.

Introduction

Major mood disorders – which include major depressive disorder and bipolar disorder – are common, cause disability and incur high cost to society (Herrman et al., 2022). They tend to run in families and first manifest in adolescence. Predicting their onsets is necessary to allow for implementation of targeted early interventions that can delay or halt progression to a mood disorder (Herrman et al., 2022). One in three offspring of parents with a mood disorder will develop mental illness by early adulthood (Rasic et al., 2014). For this reason, family history has been one of the strongest risk factors associated with major mood disorder onset. However, family history alone may not always be dependable for several reasons (McGorry, 2013). Firstly, family history is not always available since individuals could be adopted and not know their family history, making this information unavailable. Secondly, even when family history is available, it is not always reliable due to stigma associated with mental illness (Clark et al., 2022). Thirdly, not all those with a positive familial history of mood disorders will develop an illness (Al-Chalabi & Lewis, 2011). These reasons make it important to find subject specific features that can be used to complement familial history and enable more accurate prediction of mood disorder onsets.

Major depressive disorder (MDD), generally known as depression, is one of the most common psychiatric disorders and is ranked as the leading cause of disability worldwide (Herrman et al., 2022). While depression is heterogeneous in terms of levels of severity, duration and symptom profiles, its common defining features include persistent depressed mood, diminished interest or pleasure in activities, low energy, reduced concentration, feeling of worthlessness or excessive guilt, suicidal thoughts and behaviours, and substantial changes in

appetite and sleep (American Psychiatric Association & American Psychiatric Association, 2013).

Bipolar disorder (BD) is characterised by depressive and manic episodes (Hirschfeld, 2014). Depression episodes in BD present with similar characteristics to those of MDD described above. Mania is defined by increased energy, elated or irritable mood, inflated self-esteem, distractibility, reduced need for sleep, excessive activity, risky behaviour, and a flight of ideas (American Psychiatric Association & American Psychiatric Association, 2013). Typically, BD first presents as depression, and is only later diagnosed as bipolar disorder due to the occurrence of a manic episode (Hirschfeld, 2014). Most people with bipolar disorder spend more time in depressive than in the manic phases (Judd et al., 2002, 2003).

Major mood disorders run in families; offspring of parents living with major mood disorders are over four times more likely to develop a mental illness than those whose parents never had a major mood disorder (Rasic et al., 2014). Given this high familial nature of major mood disorders, a familial high risk design where offspring of parents with a major mood disorder are compared to a control group offers an opportunity to study mood disorders in their early stages (Gershon et al., 1976; Mednick & McNeil, 1968)

The diagnosis of major mood disorders is preceded by subthreshold symptoms, termed antecedents, that present early in life and continue into adulthood (Duffy et al., 2010; Pine & Fox, 2015). These antecedents are not confined to a single disorder, but shared among major mood disorders (Faedda et al., 2015; Zwicker et al., 2020). The antecedents that are most

predictive of future development of mood disorders include depression symptoms, anxiety symptoms, psychotic symptoms and basic symptoms (Rice et al., 2017; Uher et al., 2014; van Lang et al., 2007). Tracking these antecedents is therefore a useful way to understand the development of mood disorders.

Mood Disorders and Functional Connectivity

Previous neuroimaging research has investigated mood disorders by studying functional networks during the resting state, when a participant lies in the scanner doing no focused task, as well as during a task-based design, where a participant is presented with a task to complete (Stevens, 2016). Resting state connectivity, however, has appealed to scientists since (1) it enables the examination of the entire brain, (2) the fact that there is no cognitive demands during the MRI session makes it accessible to a wider and broader population, including infants, (3) and it promotes reproducibility since results are easily comparable across studies (Friston, 2011; Woodward & Cascio, 2015). From resting state research, functional networks have been identified, which are brain regions that show correlated neural activity (Friston, 2011). Though these functional networks are interconnected, specific networks have been shown to play specific roles in cognition and behaviour (Biswal et al., 1995; Dosenbach et al., 2007; Stevens, 2016)

Previous research shows that connectivity in the functional networks of people with a major mood disorder differs from that of controls, which is interpreted to mean that these dysregulations might drive the behavioural symptoms present in mood disorders (Goldstein-Piekarski et al., 2022; Price & Drevets, 2012). Several lines of research support this interpretation: (1) Genetic studies show that most mood disorder genetic variants are located in

neurons, (2) dysfunction in brain networks is implicated in neurodegenerative diseases, (3) as well as in lesion studies (Burton et al., 2007; Jobson et al., 2021; Wray et al., 2018).

People living with major mood disorders have atypical functional connectivity patterns in multiple networks (Dai et al., 2019; Yoon et al., 2020). Among the brain networks, the default mode network (DMN), which shows heightened connectivity in the absence of a task and negative correlation with networks active during task performance, has received the most attention (Raichle et al., 2001). This is because the DMN is (1) involved in internal thought processes involving the self, specifically negative thought processes and rumination (Andrews-Hanna et al., 2014), which are associated with mood disorder symptomatology, and (2) its dysfunction is implicated in major mood disorders (Broyd et al., 2009; Mulders et al., 2015a; Whitfield-Gabrieli & Ford, 2012a). The DMN is characterised by the anterior region, whose seed node is the medial prefrontal cortex, and the posterior region, whose seed node is the posterior cingulate cortex. These two regions, along with the inferior parietal lobule, are the key regions that consistently define the DMN (Andrews-Hanna et al., 2010; Buckner et al., 2008; Greicius et al., 2003)

Default Mode Network and Psychopathology

Since mood disorders run in families, using case-control study designs, as well as familial risk designs, where those at high familial risk are compared to controls with low familial risk, has been useful for investigating connectivity patterns related to mood disorders. Previous studies have provided inconsistent findings of DMN connectivity profile in major mood disorders. For one, DMN hyperconnectivity has been associated with depression (Broyd et al.,

2009; Zhao et al., 2019; Zovetti et al., 2020), while others have found reduced or no differences in DMN connectivity in major mood disorders (Pannekoek et al., 2014; Tahmasian et al., 2013).

Other researchers have also noted this, arguing that these discrepancies result from the use of differing sample sizes, acquisition parameters, analytical methods, as well as inclusion of participants at varying age ranges and illness severity (Gong & He, 2015; Mulders et al., 2015a; Nazarova et al., 2022; Qu et al., 2021). And although studying connectivity in illness is worthwhile, it is equally important to investigate connectivity patterns in a familial risk group and understand what connectivity patterns might precede illness onset. This is because (1) by the time mood disorders are diagnosed, it is already too late to successfully provide interventions and (2) mood disorders present early, albeit with subthreshold symptoms, and we can track their development through familial risk designs (Berk et al., 2010; McGorry et al., 2010).

In the study of DMN activity in familial risk groups, there have been contradictory findings. Heightened within-DMN connectivity is found among individuals with high familial risk (Posner et al., 2016), while others have reported no differences in DMN connectivity of a familial high risk group (Chai et al., 2016; Heinze et al., 2020)

The varying results seen in studies looking at DMN connectivity in a familial risk group can be attributed to differences in sample sizes, inclusion or exclusion of participants with a mood disorder diagnosis, differing age ranges of the participants, use of differing regions to define the DMN, and varying definitions of what constitutes as familial risk for a mood disorder (Chai et al., 2016; Heinze et al., 2020; Posner et al., 2016) (See Table 1). Since previous research provides inconclusive findings on the nature of DMN connectivity in illness and in familial high

risk cohorts, there is a need to investigate DMN connectivity in a familial risk cohort.

In the current study, we examine DMN connectivity in a familial risk group. We characterize the DMN using its hub nodes in the prefrontal and posterior cortex, which is where we would expect to see the most activity in this network (Barabási, 2009; van Oort et al., 2014). Major mood disorder participants are those with a parent(s) with either bipolar disorder, or depression. This definition is informed by prior research which shows that depression and bipolar disorder are very similar in their early symptoms, and that offspring of parents with a mood disorder are at higher risk of developing depression and bipolar disorder (McGuffin et al., 2003). Control participants have no family history of a major mood disorder. Lastly, we select participants who are at an age range where there is the highest risk of onset and the brain is rapidly developing (9-19), which allows us to study depression symptoms and their relation to DMN connectivity (Herrman et al., 2022).

Methods

Participants

Participants in this study include offspring of biological parent(s) with a lifetime diagnosis of a major mood disorder (FHR), as well as participants from control families (Controls) who don't have any history of a major mood disorder, matched on socio-economic status. All participants were recruited as part of the FORBOW – Families Overcoming Risk and Building Opportunities for Wellbeing – study, a longitudinal study enriched for children of parents with mental illness (Uher et al., 2014). The FHR participants were recruited by referral from adult mental health services, or from clinicians who were treating the parent(s), while the Controls

were recruited from schools and communities in Nova Scotia that matched the socioeconomic status and age of FHR participants.

Inclusion Criteria:

FHR participants were included for analysis if they had a biological parent(s) with a lifetime diagnosis of a major mood disorder (depression, bipolar disorder or schizoaffective disorder) as defined in the Diagnostic and Statistical Manual, Fifth Edition (American Psychiatric Association & American Psychiatric Association, 2013). Control participants were included if they did not have a family history of major mood and psychotic disorders.

All participants were included for analysis if they were between the ages of 9 and 19.

Exclusion Criteria:

All participants were excluded from the study if they had any clinical diagnosis of neurological disorders; a history of head trauma with loss of consciousness; and any contraindications to the MRI.

Research Ethics

The FORBOW study has been approved by the Nova Scotia Health Authority Research Ethics Board. Written informed consent was obtained from all participants (or their parents or legal guardians) prior to the study.

Behavioural Measurements

Baseline:

Parent interview: Parents were assessed by trained mental health assessors using the Structured Clinical Interview for DSM-5 Disorders (SCID-5) (Spitzer et al., 1992). The reports of the SCID were then discussed at a consensus meeting with a psychiatrist, and a final mood disorder diagnosis was made.

Offspring interview: For offspring age < 18 years, diagnostic interviews were done by trained mental health assessors blind to parent psychopathology using the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (K-SADS-PL), while for those age > 18, the SCID was used (Kaufman et al., 1997; Spitzer et al., 1992). Similar to parent assessments, the reports from these interviews were taken to a consensus meeting with a psychiatrist (who was blind to parent diagnosis) where a mood disorder diagnosis was made.

Clinical Measures: Depression symptoms were measured using the Youth Experience Tracker Instrument, YETI , a 26-item self-report questionnaire that tracks antecedent symptoms in youth (Patterson et al., 2021). The YETI has been shown to have a high degree of validity, and its depressive symptom items correlate strongly with other validated measures used in clinical practice (Angold et al., 1995; Patterson et al., 2021). Every participant completed the YETI before proceeding to their MRI scan session. Since antecedent depressive symptoms are one of the common predictors of progression to major depressive disorder and bipolar disorder, we used the antecedent depressive symptom items (max score=12) as the antecedents of interest (Durdurak et al., 2022; Pine et al., 1999; van Lang et al., 2007). For more details on the YETI,

see Appendix A.

Demographic measures: Demographic measurements including sex, age, ethnicity, height (cm) and weight (kg) were collected. Socioeconomic status was scored (range: 0-5) based on (i) maternal and (ii) paternal levels of education, (iii) family household annual income , (iv) ownership of primary residence and (v) ratio of bedrooms to residents in household (Drobinin et al., 2020; MacKenzie et al., 2017). Full scale intelligence quotient (FSIQ) scores were also measured using the Wechsler Abbreviated Scale of Intelligence (Wechsler, 2011)

MRI Acquisition

Participants were scheduled for a scanning session at the Biomedical Translational Imaging Centre at the Queen Elizabeth II Health Sciences Centre in Halifax, Nova Scotia. Prior to the scan, participants were safety screened by a MRI technologist for any MRI contraindications.

At the beginning of the scan session, participants were fitted with some padding around the head coil to minimize head movement. They were also instructed to remain motionless, keep their eyes closed and think of nothing in particular. The scan session lasted approximately 35 minutes, during which anatomical and resting state images were acquired using a 3T General Electric Discovery MR750 scanner equipped with a 32-channel head coil.

T1-weighted anatomical images (168 slices, 224×224 voxels, $1mm^3$ isotropic resolution) were acquired. T2-weighted images were also acquired at the same resolution and voxel size (repetition time = 5100ms). For more details, see Drobinin et al., 2020, 2021. After the

anatomical scans, an 8 minute resting state functional EPI scan was acquired (51 axial-oblique slices, $3mm^3$ voxels, slice thickness = 3mm with no gap, repetition time = 950ms, echo time = 3ms, flip angle = 60 degrees, multiband factor = 3).

Follow-up

Parent and offspring interviews were conducted yearly as long as the participants remained in the study. Similarly, demographic measures were also collected at the yearly follow-up, with the exclusion of IQ scores, which were only recorded at baseline.

Study participants were scheduled for an MRI scan during the yearly follow-ups. Additionally, a reliability scan was collected for some participants, usually two weeks after their yearly scan.

fMRI Preprocessing

fMRI preprocessing was done in fMRIPrep 20.2.1 (Esteban, Markiewicz, et al. (2018); Esteban, Blair, et al. (2018); RRID:SCR_016216), which is based on Nipype 1.5.1 (Gorgolewski et al. (2011); Gorgolewski et al. (2018); RRID:SCR_002502).). For a detailed description of the steps involved, see Appendix B: FMRI Preprocessing Results.

fMRI Connectivity Analysis

Connectivity analysis was completed with a custom python script using the Niearn libraries.

Regressor Selection

Using Nilearn, we followed the Friston-24 model to minimise noise signals resulting from head movement (Abraham et al., 2014; Power et al., 2012a, 2014; Satterthwaite et al., 2013). The steps for this analysis included: (i) regression of six parameters obtained by head motion correction and (ii) regression of the white matter (WM) and cerebrospinal fluid (CSF) signal averaged from WM and CSF brain regions. First order derivatives ($R^{'}$) and their squares (R^2) for white matter and cerebrospinal fluid signals were also included as regressors. These preprocessing steps are effective in reducing variance that is unlikely to reflect neural activity (Fox & Raichle, 2007).

Since head motion is a major concern in functional connectivity (Power et al., 2012a), and specifically for a pediatric cohort, we also denoised the individual data using the scrubbing method, which censors timepoints (i.e., TRs) where framewise displacement > 0.3mm (Power et al., 2014; Yan et al., 2019) or standardized DVARS > 3 (Power et al., 2012b). Following this step, we calculated the mean framewise displacement (FD) of all subjects across the entire resting state scan period (i.e., 8 mins). We excluded participants with excessive motion (mean FD > 0.4mm) from further analysis (Zheng et al., 2022).

DMN ROI Definition

For this study, we used the dorsal medial prefrontal cortex (dMPFC) and the posterior cingulate cortex (PCC) to characterise default mode network (DMN) connectivity. The PCC is a key node hub of the DMN, and the dMPFC is prominent for its association with self-referential mental processes characteristic of mood disorders (Gusnard & Raichle, 2001) For each

participant, 2 nodes of the DMN were defined using 6mm radius spheres centered on the coordinates of the dMPFC and PCC that were drawn from J. D Power's seminal paper that divided the whole brain into functional networks (Power et al., 2011). These coordinates have also been used by a recent relevant paper examining functional connectivity between the frontoparietal and default mode networks (Qu et al., 2021). These two ROIs were created in Nilearn using NiftiSpheresMasker at a spherical radius of 6mm around the ROI coordinates.

Extracting Estimates of Functional Connectivity

Functional connectivity during rest was measured as the temporal correlation of BOLD (Blood-Oxygen-level-Dependent) signal activities within the DMN. Pearson r correlations were calculated between mean timeseries for all voxels in each ROI for each individual subject.

99 scans were excluded from the analysis: 53 scans images didn't pass visual inspection; 43 scans had excessive motion (mean FD > 0.4mm) (Zheng et al., 2022); 3 participants had missing depression scores.

Statistical Analyses

First, we performed a test-retest reliability for the DMN ROIs to determine reliability measures. We then ran a mixed-effects model to test for the effects of familial risk on default mode network connectivity. We also included age and sex as fixed effects since these have been shown to influence functional connectivity (Chai et al., 2016; Sanders et al., 2023; Shapero et al., 2019; Stevens, 2016; Teeuw et al., 2019). Additionally, we included family and participant identifiers as random effects in the model to account for the fact that some participants are

siblings and some participants have repeat measurements (Durdurak et al., 2022; Teeuw et al., 2019). As a follow up step, we performed a sensitivity analyses to rule out any effects that could be driven by motion, IQ, an anxiety diagnosis, or socioeconomic status (Durdurak et al., 2022; Finn et al., 2015; Meier et al., 2018; Sripada et al., 2014; Van Dijk et al., 2012). Finally, since some participants had a diagnosis of a major mood disorder in follow up sessions, we also included diagnosis as a covariate in the sensitivity analyses (Öngür et al., 2010; Scalabrini et al., 2020; Yan et al., 2019; Zhang et al., n.d.).

To examine the correlation between default mode network connectivity and depression symptoms, we regressed out age from both variables for comparability, normalized the variables, and then ran a repeated measures correlation (Bakdash & Marusich, 2017).

Post-hoc Analyses

We ran a linear mixed model analysis to investigate whether familial risk, depressive symptoms or a mood disorder diagnosis independently influence DMN functional connectivity. Additionally, we ran a mixed effect analysis to investigate whether, in addition to familial risk, depressive symptoms or a mood disorder diagnosis influence functional connectivity.

Results

The participants included for analysis are summarized in Table 3. The groups had an equal distribution of males and females, and depression symptoms did not vary across groups. The IQ scores for both groups were very similar. However, since we have more familial high risk participants, comparison of IQ across both groups shows significant differences. 32 participants

have a mood disorder diagnosis, most of whom are females, with majority of them being in the familial high-risk group. There was no significant difference in mean FD between the two groups (FHR group: 0.148 ± 0.08; Control group: 0.156 ± 0.08; $p = 0.23$, two-sample t test).

Test-retest Reliability

We calculated fair test-retest reliability for PCC-to-dMPFC connectivity (ICC = 0.629, 95% CI [0.32, 0.485]) and poor test-retest reliability across the default mode network (ICC = 0.39, 95% CI [0.217, 0.55]). These measures are at par with the Human Connectome Project's reliability measures, from which our analysis pipeline is derived (Noble et al., 2019; Van Essen et al., 2013).

DMN Functional Connectivity in Controls and FHR

First, we tested whether DMN connectivity was different in the familial high risk and control groups. We first regressed age out of functional connectivity and found no differences in connectivity between the two groups ($p > 0.05$) (Figure 1). To rule out whether mood disorder diagnosis influenced the results, we plotted participants with a diagnosis as a separate group. We found that the results remained the same (Figure 2). Linear mixed model analysis showed that DMN connectivity did not differ across both groups ($B = -0.009$, $SE = 0.02$, $p > 0.05$) (Table 4). To identify any effects from other covariates (anxiety diagnosis, mood disorder diagnosis, motion, socioeconomic status, IQ), we performed a sensitivity analysis and found that only age had a significant influence on DMN connectivity (Table 5).

Depression Symptoms in Controls and FHR

We performed exploratory analysis to investigate the trend of depression symptoms in FHR and controls. We found that, in both groups, depression symptom scores increased over age (Figure 3). Stratification of the groups by gender showed that this increase was driven by females (Figure 4).

Association of DMN Connectivity and Depression Symptoms

To test whether DMN connectivity was associated with depression symptoms, we performed a repeated measures correlation. We did not find a significant association between DMN connectivity and depression symptoms in Controls (r (74) = -0.18, $p > 0.05$) or FHR (r (164) = 0.06, $p > 0.05$) (Figures 5 and 6).

Effects of Familial Risk, Clinical Risk and Mood Disorder Diagnosis on Functional Connectivity

There was no significant influence of familial risk (Table 6), clinical risk (Table 7) or diagnosis (Table 8) on DMN connectivity. Also, when either clinical risk or a mood disorder diagnosis are included as covariates in addition to familial risk, they do not significantly influence DMN connectivity (Tables 9 and 10).

Discussion

We set out to investigate DMN connectivity in young people at familial risk for major mood disorders and characterise the association between DMN connectivity and depression symptoms. Our findings show that there are no differences in DMN connectivity between the FHR and control groups. Additionally, we show that there are differing trends in the association between DMN connectivity and depression symptoms for the controls versus FHR groups; controls show a weak negative correlation, while FHR show a weak positive correlation.

We found no significant differences in DMN connectivity between participants at familial risk for major mood disorders versus controls. These results are consistent with what a few investigations have reported (Chai et al., 2016; Heinze et al., 2020), but disagree with another study that found increased connectivity in FHR participants relative to controls (Posner et al., 2016). Some studies have also reported increased connectivity in participants with major mood disorders (Zhao et al., 2019; Zovetti et al., 2020), as well as reduced or no differences between participants with major mood disorders and those without (Pannekoek et al., 2014). By including participants with a mood disorder diagnosis, this study was able to examine whether DMN connectivity is associated with familial risk irrespective of illness; accounting for diagnosis in the sensitivity analysis ruled out any differences that could be driven by participants with a mood disorder. Additionally, an exploratory analysis of DMN connectivity including participants with a mood disorder as an independent group showed that there was no difference between the groups (Figure 2). Our findings, and the diverging findings from other researchers might mean that there is no detectable signal in the DMN that can distinguish those with a mood disorder, or at familial risk, from controls. This would then mean that DMN connectivity might not be a

reliable biomarker associated with familial risk, or mood disorders. For future studies, it would be worthwhile to incorporate advanced techniques that take into account the BOLD signals from the entire brain, like brain age gap, since these show promise of providing reliable and consistent findings (Lund et al., 2021).

We found that both groups had increasing depression symptom scores over age, and that this increase was driven by females. This finding is consistent with previous literature which shows that depressive symptoms are more prevalent in females, and that mood disorders are twice as common in females (Angold et al., 2002; Eaton et al., 2012; Padgaonkar et al., 2020). Interestingly, control females had slightly higher depression symptom scores over time than FHR, which can be explained by the facts that (1) there are fewer controls at later ages, and that (2) most of the controls with a mood disorder diagnosis are at later ages. This is a limitation of our cohort, since there is a selection bias: over time, FHR participants remain in the study at a higher rate than controls. A balanced sample would be appropriate as it would allow us to better interpret these results.

We found differential associations between DMN connectivity and depression symptoms in the FHR versus control groups. These results build on previous research which shows that there is a positive correlation between DMN connectivity and depression symptoms in the familial high risk group (Chai et al., 2016), as well as in psychopathology (Ghaznavi et al., 2023; Zhu et al., 2017). However, caution must be taken to interpret these results since the associations are weak, and they do not meet statistical significance. Future studies are needed to validate this trend in a larger sample.

Conclusion

We found no differences between DMN connectivity in a familial risk versus a control group, which indicates that DMN connectivity may not be a risk factor associated with familial risk. Increased depression symptoms scores, specifically in females, may be useful for offering targeted interventions in both FHR and control groups. However, the lack of significant associations between DMN connectivity and depression symptoms indicates that DMN connectivity might not underlie depressive symptoms; future research using advanced techniques, with a longitudinal design and a larger sample, is needed to validate these results.

Tables and Figures for Chapter 2

	Posner et al., 2016	**Chai et al., 2016**	**Heinze et al., 2020**
Sample size	104	43	210
Included participants with a mood disorder	Yes	No	No
Participants age range	11-60	8-14	15-27
DMN regions used	Lateral parietal lobe, Posterior cingulate cortex	Medial prefrontal cortex, Posterior cingulate cortex	Right angular gyrus
Familial risk definition	FHR as participants of parents/grandparents with depression	FHR as participants of parents with depression	FHR as participants with family members with bipolar 1 disorder

Table 1. Summary of previous studies on DMN connectivity in familial risk groups

Regions	**Abbreviation**	**Coordinates (*x, y, z*)**
Dorsal medial prefrontal cortex	dmPFC	-7, 46, 35
Posterior cingulate cortex	PCC	0, -52, 30

Table 2. Regions used to define the DMN

Table 3. Demographic and clinical characteristics of participants by family group

		Controls (n=78)	FHR (n=126)	*p* value
Sex (Fem/M)		38/40	61/65	1.0[a]
Age (years)		13.22 (2.65)	13.42 (2.91)	0.59[b]
IQ		109.38 (12.64)	104.54 (14.00)	0.02[b]
YETI Score		1.46 (2.88)	1.67 (2.68)	0.55[b]
Mood Disorder Diagnosis		6 (Fem = 4)	26 (Fem = 16)	
Scans	Initial	78	126	
	Follow up	75	165	

Note: All quantitative data are expressed as mean ± standard deviation; for sex data, sample size is presented here; due to 6 missing IQ values, the mean and standard deviation presented here are for 121 FHR and 77 Control participants; Follow up scans also includes reliability scans
Abbreviation: YETI; Youth Experience Tracker Instrument; FHR, Familial High Risk; Fem, Females; M, Males

[a] ρ values were obtained by a chi-square test

[b] ρ value was obtained by a two-sample t-test

Table 4. Linear mixed model analysis results showing the fixed effects of age, sex, familial risk and clinical risk, as well as random effects of family (fid) and individual (iid) on DMN functional connectivity

	DMN Functional Connectivity		
Predictors	***Estimates***	***CI***	***p***
(Intercept)	0.302	0.179 – 0.425	**<0.001**
Group	-0.009	-0.064 – 0.047	0.762
Age	0.011	0.004 – 0.019	**0.005**
Sex	-0.025	-0.075 – 0.025	0.325
Random Effects			
σ^2	0.02		
$\tau_{00\ iid}$	0.01		
$\tau_{00\ fid}$	0.01		
N_{fid}	132		
N_{iid}	203		

Note: 444 total observations for DMN functional connectivity. Marginal R^2 is 0.028.

Table 5. Sensitivity analysis testing for the effects of anxiety diagnosis, mood disorder diagnosis, SES, IQ, and motion on DMN functional connectivity

	DMN Functional Connectivity		
Predictors	***Estimates***	***CI***	***p***
(Intercept)	0.188	-0.062 – 0.439	0.141
Group	-0.000	-0.057 – 0.057	0.999
Age	0.013	0.004 – 0.022	**0.004**
Sex	-0.019	-0.069 – 0.032	0.467
Anxiety Diagnosis	0.024	-0.024 – 0.073	0.323
Mood Disorder Diagnosis	-0.016	-0.083 – 0.052	0.643
Motion	0.128	-0.137 – 0.393	0.344
SES	0.010	-0.009 – 0.030	0.293
IQ	0.000	-0.002 – 0.002	0.874
Random Effects			
σ^2	0.02		
$\tau_{00\ iid}$	0.01		
$\tau_{00\ fid}$	0.01		
$N_{\ fid}$	128		
$N_{\ iid}$	197		

Note: 434 total observations for DMN functional connectivity. Marginal R^2 is 0.037. (10 observations were dropped from analysis due to missing IQ values)

Table 6. Post-hoc analysis testing for the effects of familial risk, age and sex on DMN functional connectivity

	DMN Functional Connectivity		
Predictors	***Estimates***	***CI***	***p***
(Intercept)	0.302	0.179 – 0.425	**<0.001**
Group	-0.009	-0.064 – 0.047	0.762
Age	0.011	0.004 – 0.019	**0.005**
Sex	-0.025	-0.075 – 0.025	0.325
Random Effects			
σ^2	0.02		
$\tau_{00\ iid}$	0.01		
$\tau_{00\ fid}$	0.01		
N_{fid}	132		
N_{iid}	203		

Note: 444 total observations for DMN functional connectivity. Marginal R^2 is 0.028.

Table 7. Post-hoc analysis testing for the effects of clinical risk, age and sex on DMN functional connectivity

	DMN Functional Connectivity		
Predictors	***Estimates***	***CI***	***p***
(Intercept)	0.297	0.179 – 0.416	**<0.001**
Depression Symptoms	0.001	-0.006 – 0.007	0.861
Age	0.011	0.003 – 0.019	**0.006**
Sex	-0.025	-0.075 – 0.026	0.335
Random Effects			
σ^2	0.02		
$\tau_{00\ iid}$	0.01		
$\tau_{00\ fid}$	0.01		
N_{fid}	132		
N_{iid}	203		

Note: 444 total observations for DMN functional connectivity. Marginal R^2 is 0.028.

Table 8. Post-hoc analysis testing for the effects of mood disorder diagnosis, age and sex on DMN functional connectivity

	DMN Functional Connectivity		
Predictors	***Estimates***	***CI***	***p***
(Intercept)	0.295	0.173 – 0.417	**<0.001**
Mood disorder diagnosis	-0.006	-0.070 – 0.059	0.861
Age	0.012	0.003 – 0.020	**0.007**
Sex	-0.025	-0.076 – 0.025	0.318
Random Effects			
σ^2	0.02		
$\tau_{00\ iid}$	0.01		
$\tau_{00\ fid}$	0.01		
N_{fid}	132		
N_{iid}	203		

Note: 444 total observations for DMN functional connectivity. Marginal R^2 is 0.027.

Table 9. Post-hoc analysis testing for the effects of clinical risk, familial risk, sex, and age on DMN functional connectivity

	DMN Functional Connectivity		
Predictors	***Estimates***	***CI***	***p***
(Intercept)	0.302	0.179 – 0.425	**<0.001**
Depression Symptoms	0.001	-0.006 – 0.007	0.853
Group	-0.009	-0.064 – 0.047	0.759
Age	0.011	0.003 – 0.019	**0.006**
Sex	-0.025	-0.075 – 0.026	0.339
Random Effects			
σ^2	0.02		
$\tau_{00\ iid}$	0.01		
$\tau_{00\ fid}$	0.01		
N_{fid}	132		
N_{iid}	203		

Note: 444 total observations for DMN functional connectivity. Marginal R^2 is 0.028.

Table 10. Post-hoc analysis testing for the effects of mood disorder diagnosis, familial risk, age, and sex on DMN functional connectivity

	DMN Functional Connectivity		
Predictors	***Estimates***	***CI***	***p***
(Intercept)	0.300	0.173 – 0.427	**<0.001**
Mood disorder diagnosis	-0.004	-0.070 – 0.061	0.896
Group	-0.008	-0.064 – 0.048	0.780
Age	0.012	0.003 – 0.020	**0.007**
Sex	-0.025	-0.075 – 0.025	0.322
Random Effects			
σ^2	0.02		
$\tau_{00\ iid}$	0.01		
$\tau_{00\ fid}$	0.01		
N_{fid}	132		
N_{iid}	203		

Note: 444 total observations for DMN functional connectivity. Marginal R^2 is 0.028.

Figure 1. Default Mode Connectivity in Controls and FHR youth

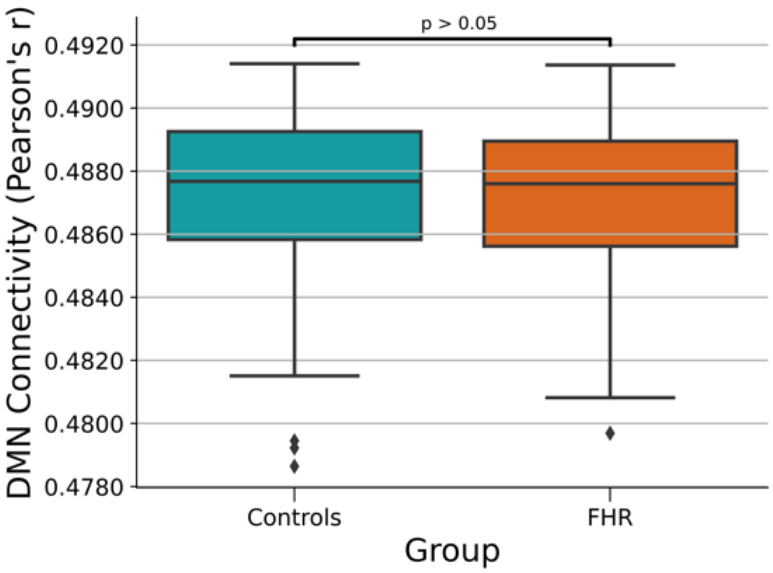


Figure 2. Default Mode Connectivity in Controls, FHR and youth with a mood disorder diagnosis

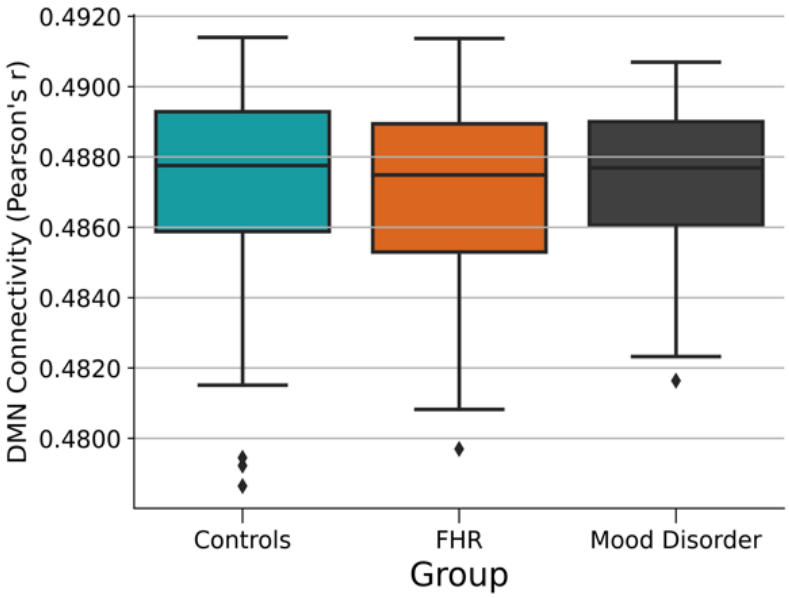


Figure 3. Depression symptom scores in Controls and FHR youth

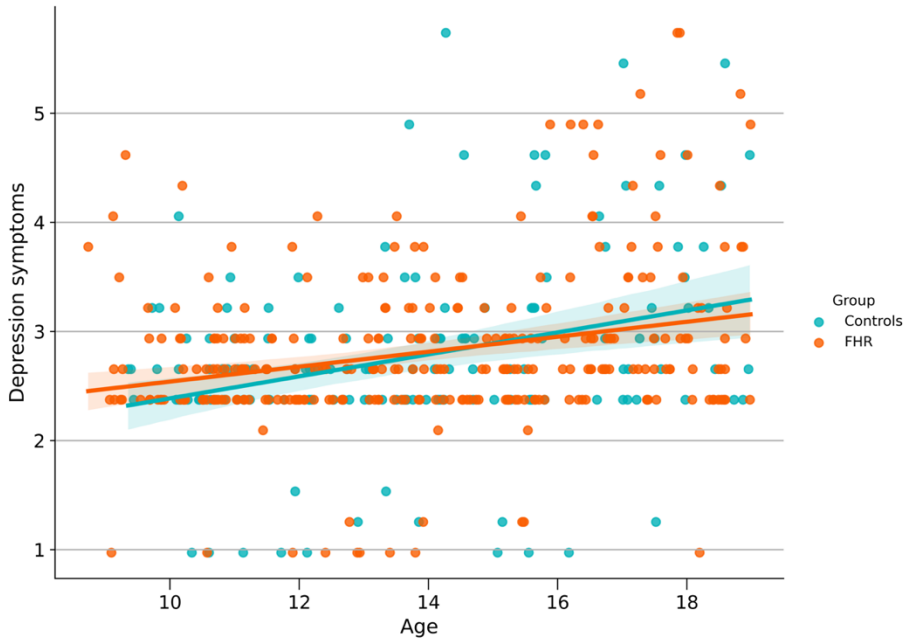


Figure 4. Depression symptom scores by sex in Controls and FHR

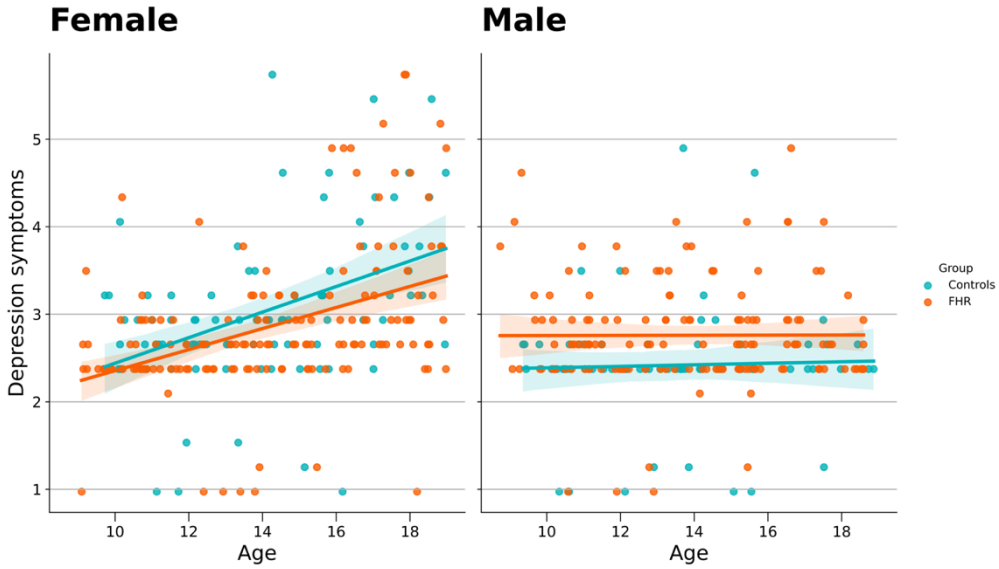


Figure 5. Correlation of DMN connectivity and depression symptoms in Controls

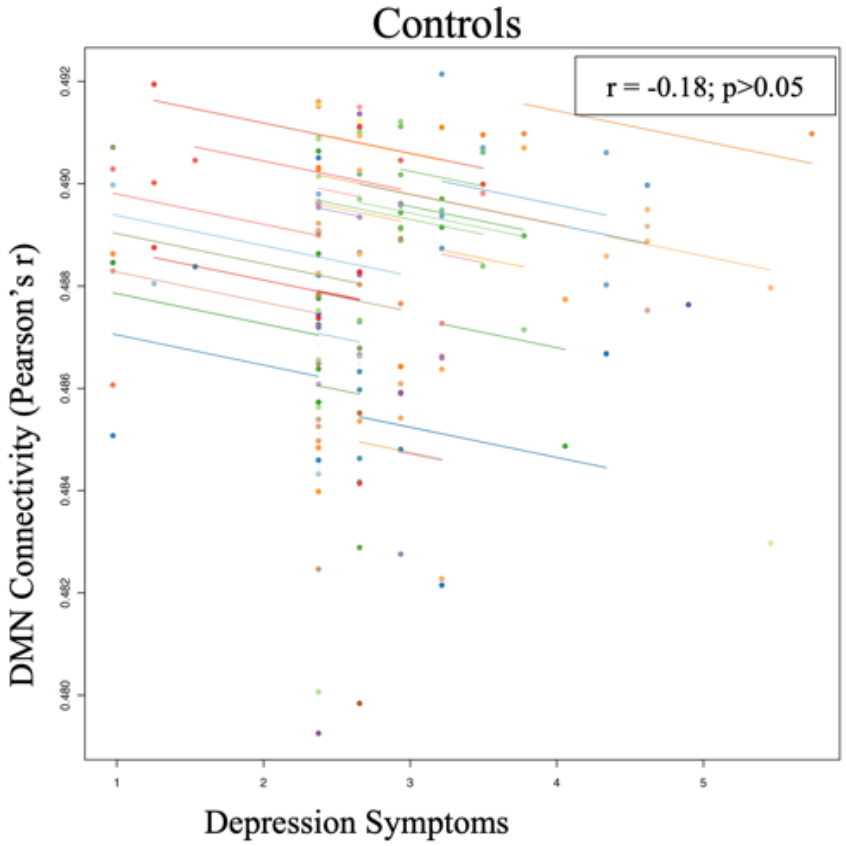
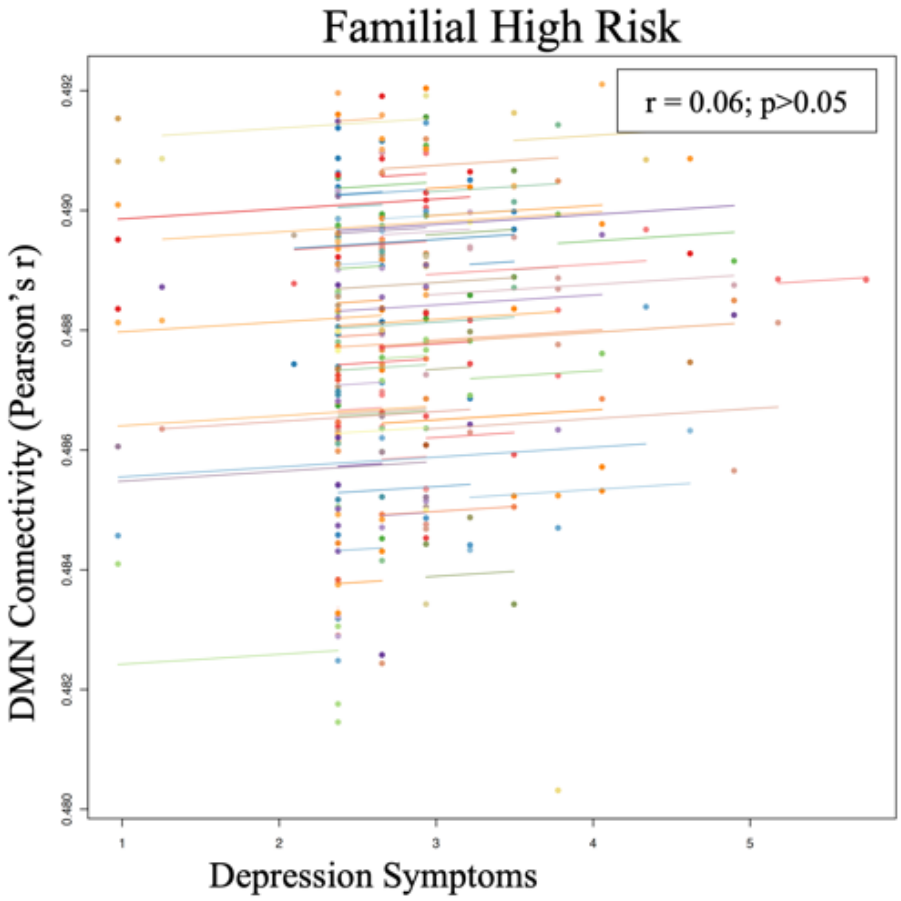


Figure 6. Correlation of DMN connectivity and depression symptoms in FHR



CHAPTER 3: FROM CONNECTIVITY AND ITS ASSOCIATION WITH FAMILIAL RISK AND CLINICAL RISK TO CONNECTIVITY AND ITS ASSOCIATION WITH MOOD DISORDER ONSET.

In the first project, we found that connectivity was not significantly associated with familial risk or clinical risk in a risk enriched cohort. For the second project, we decided to investigate connectivity further and test whether it is associated with the onset of mood disorders of participants in our cohort. This was motivated by the fact that, (1) though familial risk is a strong risk factor for mood disorder onsets, familial information is not always available, so using subject specific variables, like neural indicators, in addition to family history would be useful, (2) family history is not a sufficient predictor, so there is need to improve prediction further, and (3) there is a need to understand mechanisms underlying risk. Therefore, we decided to study connectivity in two key networks that have been associated with mood disorders: default mode network, and the salience network. Our main goal was to understand whether default mode network, salience, and default mode network to salience network connectivity are associated with the onset of major mood disorders. We hypothesized that connectivity within and between these networks is indeed associated with mood disorder onsets and can therefore complement family history and help in better prediction of mood disorder onsets.

CHAPTER 4: FUNCTIONAL CONNECTIVITY AND ONSET OF MAJOR MOOD DISORDERS IN OFFSPRING AT HIGH FAMILIAL RISK

Abstract

Mood disorders begin in late adolescence to early adulthood, often affecting an individual over their lifetime. There is a need to predict their onsets by using risk factors associated with illness such as family history and brain connectivity. While family history is a risk factor associated with major mood disorder onsets, it is not sufficient, depends on recall, availability of family members for interviews, and willingness to share potentially stigmatizing information, and it is not always available. In addition, we need to understand the mechanisms underlying the development of risk for major mood disorders to help design effective preventive and therapeutic strategies. Therefore, we decided to investigate whether brain connectivity can complement family history. Specifically, we studied the default mode (DMN) and salience networks (SN) that are implicated in major mood disorders. These networks show differential activity in participants with mood disorders, but it is not known whether this differential connectivity precedes mood disorder onsets. Therefore, we investigated whether connectivity in these networks predicts the onset of mood disorders in a sample of youth at high familial risk for major mood disorders. The sample consisted of 204 participants (Familial High Risk (FHR): 126, Mean age=13.38, SD=2.88; Controls: 78, Mean age=13.22, SD=2.65), who completed a magnetic resonance imaging (MRI) scan and annual diagnostic interviews before and for up to 5 years after the MRI. There were 32 onsets of major mood disorders in the years following the MRI scan. We performed independent cox regression with connectivity variables of interest, as well as a multivariate analysis with all variables while controlling for sex. Cox regression showed that

only family history (hazard ratio=2.33, 95% CI=1.26-4.3) and depressive symptoms (hazard ratio=1.10, 95% CI=1.01-1.2) were positively prospectively associated with onsets. Brain connectivity variables were not associated with onsets in bivariate or multivariate analyses. These results show that functional connectivity within and between the DMN and SN does not meaningfully contribute to the prediction of mood disorders onset.

Introduction

Major mood disorders – which include major depressive disorder and bipolar disorder – are common, cause disability and incur high cost to society (Herrman et al., 2022). They tend to run in families and first manifest in adolescence. Predicting their onsets is necessary to allow for implementation of targeted early interventions that can delay or halt progression to a mood disorder (Herrman et al., 2022). One in three offspring of parents with a mood disorder will develop mental illness by early adulthood (Rasic et al., 2014). For this reason, family history has been one of the strongest risk factors associated with major mood disorder onset. However, family history alone may not always be dependable for several reasons (McGorry, 2013). Firstly, family history is not always available since individuals could be adopted and not know their family history, making this information unavailable. Secondly, even when family history is available, it is not always reliable due to stigma associated with mental illness (Clark et al., 2022). Thirdly, not all those with a positive familial history of mood disorders will develop an illness (Al-Chalabi & Lewis, 2011). These reasons make it important to find subject specific features that can be used to complement familial history and enable more accurate prediction of mood disorder onsets.

Aberrant, that is atypical, functional connectivity is associated with major mood disorders (Dai et al., 2019; Sha et al., 2019; Yoon et al., 2020). Specifically, disruptions in key default mode and salience networks have been shown in major mood disorders; these networks have been linked to key cognitive, executive and emotive functions that are disrupted in mood disorders (Menon, 2011; Palaniyappan et al., 2019). Additionally, increased salience network

connectivity in a familial risk group has been shown to predict depression at follow-up, while default mode network connectivity is altered in familial risk groups in a non-specific fashion (Pawlak et al., 2022; Piguet et al., 2015; Singh et al., 2014). These results make it worthwhile to study brain connectivity networks and their association with mood disorder onsets.

In this study, we investigate whether functional connectivity in the salience and default mode networks can improve the prediction of major mood disorder onsets.

Mood Disorders

Depression and bipolar disorder are mood disorders that begin in late adolescence to early adulthood, and they often affect individuals over their lifetime (Kim-Cohen et al., 2003). Depression presents with persistent depressed mood, diminished pleasure in activities, low energy, reduced concentration, feelings of worthlessness or excessive guilt, suicidal thoughts, and changes in appetite and sleep (American Psychiatric Association & American Psychiatric Association, 2013). Bipolar disorder is characterized by depressive symptoms, as well as manic episodes (Hirschfeld, 2014). Mania presents with increased energy, elated or irritable mood, inflated self-esteem, distractibility, reduced need for sleep, excessive activity, risky behaviour, and a flight of ideas (American Psychiatric Association & American Psychiatric Association, 2013). In addition to their shared symptoms, both disorders begin early and with very similar subthreshold symptoms. Even individuals who eventually develop bipolar disorder typically first present with depression (Hirschfeld, 2014; Judd et al., 2002, 2003). Due to the overlap in their early presentation and symptomatology, studying risk factors associated with these disorders in their early stages is a useful way to identify persons at risk. A viable risk indicator is brain

functional connectivity, which shows the correlation in Blood Oxygen Level Dependent (BOLD) activity between resting state networks (Biswal et al., 2010).

Default Mode Network

The default mode network (DMN) is a network with hub nodes in the posterior cingulate cortex and the medial prefrontal cortex (Raichle, 2015). It shows increased activity during rest when a participant lies in the scanner doing no specific focused task, and decreased activity during novel, non-self-referential, goal directed tasks. (Raichle et al., 2001; Shulman et al., 1997). Due to this increased activity during rest, the DMN is assumed to underlie internal self-directed thought processes (Raichle, 2015). Increased activity in this network is associated with mood disorders (Mulders et al., 2015b; Whitfield-Gabrieli & Ford, 2012b).

Salience Network

The salience network (SN) is a network with hub nodes in the anterior cingulate cortex and dorsal anterior cingulate cortex (Menon, 2015). It shows increased activity in response to novel salient stimuli (Menon & Uddin, 2010). Due to this increased activity towards novel stimuli, it has been suggested that the SN is responsible for (1) orienting to important information in the environment, and (2) coordinating the activity from other brain networks to guide appropriate behaviour towards the salient information (Menon & Uddin, 2010). Hypoconnectivity in this network is associated with mood disorders (Gong et al., 2019; Goodkind et al., 2015; Sha et al., 2019).

Default Mode Network to Salience Network

The salience network has a major role in regulating behaviour in response to internal, self-referential thoughts that arise from the default mode network's activity (Menon & Uddin, 2010). Aberrant connectivity of the default mode network to salience network (DMN-to-SN) connectivity has been linked with mood disorders (Mulders et al., 2015b; Price & Drevets, 2012; Sha et al., 2019). Specifically, DMN-to-SN hypoconnectivity has been associated with higher anhedonia in depression and bipolar disorder (Sharma et al., 2017; Yu et al., 2022). This disruption is suggested to reflect reduced capacity for regulation of self-referential thought processes that is evident in mood disorders (Yu et al., 2022)

This aberrant activity within the SN, DMN and between the SN and DMN is thought to relate to impaired attention and motivation that is evident in mood disorders (Seeley, 2019; Uddin, 2015).

Functional Connectivity and Mood Disorder Onset

Functional connectivity has been associated with familial risk, and may therefore be used in addition to familial risk to improve the reliability of prediction of mood disorder onsets (Chase et al., 2021). Pawlak et al., used a seed-based approach to investigate the roles of the DMN and SN in predicting onsets in a sample of 135 participants aged 11-17; they found that increased activity in the SN predicted depression onset at follow-up (Pawlak et al., 2022). Another study by Singh et al., used data-driven independent component analysis to investigate the role of DMN in 24 youth at high familial risk for major mood disorders, also finding that there was

increased DMN connectivity relative to controls (Singh et al., 2014). However, a meta-analysis of 29 studies on connectivity in familial risk offspring (with differing age ranges and analytical approaches) found that DMN connectivity was altered in a non-specific fashion – either increased or decreased – among participants at familial risk (Piguet et al., 2015; Singh et al., 2014).

In this study, we aimed to investigate whether functional connectivity can improve identification of risk for major mood disorders. We examined the relationships between DMN, SN, DMN-SN functional connectivity, familial risk, and onset of major mood disorders. We hypothesized that functional connectivity would improve prediction of major mood disorder diagnosis over using family history on its own.

Methods

Participants

Participants of the Families Overcoming Risk and Building opportunities for Wellbeing Cohort (FORBOW), a longitudinal risk-enriched cohort study that investigates risk factors for mental illness in youth (Uher et al., 2014), who were aged 9 to 19 years and did not have contraindications to MRI were invited to participate. Familial high-risk (FHR) participants included offspring of biological parent(s) with a lifetime diagnosis of a major depressive or bipolar disorder, while control participants come from families with no history of mood disorders. The FHR participants were recruited through clinical referrals, while controls were recruited from communities and schools in Nova Scotia that matched the socioeconomic status and age of FHR participants.

Inclusion Criteria

Participants were included if they were between the ages of 9 and 19.

Familial high risk participants were included in the study if they had a parent(s) with a lifetime diagnosis of a major mood disorder (depression, bipolar disorder or schizoaffective disorder) as defined in the Diagnostic and Statistical Manual, Fifth Edition (American Psychiatric Association & American Psychiatric Association, 2013). Control participants were included if they did not have any family history of major mood and psychotic disorders.

Exclusion Criteria

Participants were excluded from the study if they had a neurological disorder, a history of

head trauma with loss of consciousness, or contraindications to the MRI.

Research Ethics

The FORBOW study has been approved by the Nova Scotia Health Authority Research Ethics Board. Participants who had the capacity to decide provided a written informed consent; those who did not have the capacity to provide a full consent themselves provided an assent and their parent or guardian provided written informed consent.

Measurements

Baseline

Parent diagnostic interview: Parents were assessed by trained interviewers using the Structured Clinical Interview for DSM-5 Disorders (SCID-5) (Spitzer et al., 1992). The reports of the SCID were presented at a consensus meeting with a psychiatrist, who confirmed all diagnoses.

Offspring diagnostic interview: Trained interviewers blind to parent psychopathology completed diagnostic interviews using the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (K-SADS-PL) for participants aged < 18 years, and SCID for those age > 18 (Kaufman et al., 1997; Spitzer et al., 1992). The reports from these interviews were presented at a consensus meeting with a psychiatrist who was blind to parent diagnosis and confirmed all diagnoses.

Clinical Measures: Depression symptoms were measured using the Youth Experience Tracker Instrument, YETI , a 26-item self-report questionnaire that tracks antecedent symptoms in youth (Patterson et al., 2021). The YETI has good internal consistency and strong concurrent validity with commonly used measures of depressive symptoms (Angold et al., 1995; Patterson et al., 2021). Every participant completed the YETI before their MRI scan session. Since depression

symptoms are one of the common predictors of progression to major depressive disorder and bipolar disorder, we used the depressive symptom subscale (max score=12) as a predictor (Durdurak et al., 2022; Pine et al., 1999; van Lang et al., 2007). For more details on the YETI, see Appendix A.

Demographic and physical measures: We recorded participant sex, gender, age, race and ethnicity. We measured the participant's height (cm) and weight (kg) with calibrated scales. We scored sociodemographic status (range: 0-5) based on (i) maternal and (ii) paternal levels of education, (iii) family household annual income , (iv) ownership of primary residence and (v) ratio of bedrooms to residents in household (Drobinin et al., 2020; MacKenzie et al., 2017). We measured the Full scale intelligence quotient (FSIQ) with the Wechsler Abbreviated Scale of Intelligence (Wechsler. D., 2011).

MRI Acquisition

Participants were scheduled for scanning sessions at the Biomedical Translational Imaging Centre at the Queen Elizabeth II Health Sciences Centre in Halifax, Nova Scotia. Prior to the scan, participants were screened for MRI contraindications.

For the scan session, participants were instructed to remain motionless, keep their eyes closed and think of nothing in particular. Anatomical and resting state scans were acquired using a 3T General Electric Discovery MR750 scanner equipped with a 32-channel head coil.

T1-weighted anatomical images (168 slices, 224×224 voxels, $1mm^3$ isotropic resolution) were acquired. T2-weighted images were also acquired at the same resolution and voxel size (repetition time = 5100ms). For more details, see Drobinin et al., 2020, 2021. After the

anatomical scans, an 8 minute resting state functional EPI scan was acquired (51 axial-oblique slices, $3mm^3$ voxels, slice thickness = 3mm with no gap, repetition time = 950ms, echo time = 3ms, flip angle = 60 degrees, multiband factor = 3).

Follow-up

Parent and offspring diagnostic interviews were conducted annually as long as the participants remained in the study. Similarly, demographic measures were collected at the yearly follow-up, with the exclusion of IQ scores, which were only recorded at baseline.

Study participants were scheduled for an MRI scan during the yearly follow-ups. Additionally, a reliability scan was collected for some participants, usually two weeks after their yearly scan.

fMRI Preprocessing

fMRI preprocessing was done in fMRIPrep 20.2.1 (Esteban, Markiewicz, et al. (2018); Esteban, Blair, et al. (2018); RRID:SCR_016216), which is based on Nipype 1.5.1 (Gorgolewski et al. (2011); Gorgolewski et al. (2018); RRID:SCR_002502).). For a detailed description of the steps involved, see Appendix B: FMRI Preprocessing Results.

fMRI Connectivity Analysis

Connectivity analysis was completed with a custom python script using the Nilearn libraries.

Regressor Selection

Using Nilearn, we followed the Friston-24 model to minimise noise signals resulting from head movement (Abraham et al., 2014; Power et al., 2012a, 2014; Satterthwaite et al., 2013). The steps for this analysis included: (i) regression of six parameters obtained by head motion correction and (ii) regression of the white matter (WM) and cerebrospinal fluid (CSF) signal averaged from WM and CSF brain regions. First order derivatives ($R^{'}$) and their squares (R^2) for white matter and cerebrospinal fluid signals were also included as regressors. These preprocessing steps have been shown to be effective in reducing variance that is unlikely to reflect neural activity (Fox & Raichle, 2007).

Since head motion is a major concern in functional connectivity (Power et al., 2012a), and specifically for a paediatric cohort, we also denoised the individual data using the scrubbing method, which censors timepoints (i.e., TRs) where framewise displacement > 0.3mm (Power et al., 2014; Yan et al., 2019) or standardized DVARS > 3 (Power et al., 2012b). Following this step, we calculated the mean framewise displacement (FD) of all subjects across the entire resting state scan period (i.e., 8 mins). Participants with excessive motion (mean FD > 0.4mm) during the scan period were also excluded from analysis (Zheng et al., 2022). There was no significant difference in mean FD between the two groups (FHR group: 0.149 ± 0.07; Control group: 0.156 ± 0.08; $p > 0.05$, two-sample t test).

DMN and SN ROI Definition

We used the dorsal medial prefrontal cortex (dMPFC) and the posterior cingulate cortex (PCC) to characterise DMN connectivity, and the dorsal anterior cingulate (dACC) cortex and anterior insula (AI) to define the SN. The PCC is a key node hub of the DMN, and the dMPFC is

prominent for its association with self-referential mental processes characteristic of mood disorders (Gusnard & Raichle, 2001). The dACC and AI are hub nodes of the SN, which plays a role in orienting us towards important external information and internal events, and dysregulation of this network is related to cognitive deficits in mood disorders (Buckholtz & Meyer-Lindenberg, 2012; Menon, 2011; Uddin, 2015). For each participant, 2 nodes of the DMN and 2 nodes of the SN were defined using 6mm radius spheres centered on the coordinates of the dMPFC, PCC and dACC, AI respectively. These coordinates were drawn from J. D Power's seminal paper that divided the whole brain into functional networks (Power et al., 2011). The four ROIs were created in Nilearn using NiftiSpheresMasker, at a spherical radius of 6mm around the ROI coordinates (Table 11).

Extracting Estimates of Functional Connectivity

Functional connectivity during rest was measured as the temporal correlation of BOLD (Blood-Oxygen-level-Dependent) signal activities within the DMN and SN. Pearson r correlations were calculated between mean timeseries for all voxels in each ROI for each individual subject.

We excluded 96 scans from the analysis: 53 scan images didn't pass visual inspection and 49 scans had excessive motion (mean FD > 0.4mm) (Zheng et al., 2022).

Statistical Analyses

To determine the association between DMN, SN, DMN-to-SN functional connectivity, familial risk, and onset of major mood disorders, we ran a Kaplan-Meier estimation using

survminer (Kassambara et al., 2021) and *survival* (Therneau, 2020) packages, and Cox proportional hazards regression (*coxme* package) in R (Therneau, 2022). We used age as the survival time in all models, and DMN, SN, DMN-to-SN connectivity, and sex as independent variables in the Cox model. To check that the Cox proportional hazards model did not violate the proportional hazards assumption, we plotted Schoenfeld residuals for each covariate included in the Cox regression model. We also included family and participant ID as random effects in the model to account for the relatedness of participants and the fact that some participants had repeated measurements (Durdurak et al., 2022; Teeuw et al., 2019). Mood disorder diagnosis from follow-ups was the primary outcome. We first performed bivariate analysis to test the independent effects of each of DMN, SN, and DMN-to-SN functional connectivity on onsets of major mood disorders. In a second step, we included familial risk, depression symptoms and socioeconomic status as covariates. Finally, we performed a multivariate analysis using DMN, SN, DMN-to-SN connectivity, in addition to familial risk, depression symptoms, and socioeconomic status as covariares of interest. All models also accounted for survival time (age), and sex. The functional connectivity scores were standardized so that hazard ratios represent the increase of a one standard deviation in connectivity.

Results

Table 12 describes the characteristics of included participants by family history group. Two thirds of the participants were offspring of a parent(s) with a major mood disorder. Both groups had a balanced distribution of females and males, with the number of familial high-risk participants being almost twice that of control participants. Thirty two participants had a new mood disorder diagnosis at one of the follow-up assessments, with majority of them being

female, and in the familial risk group.

Survival Curves

To investigate the distribution of mood disorder onsets across age and family history groups, we plotted survival curves to visualize the progression to onsets in the two groups (Figure 7). At age 9, both groups start out with zero onsets, but over time, the proportion of mood disorder onsets increases. At age 15, the proportion of onsets in the familial high-risk group surpasses that of controls, and by about age 17, 50% of the FHR participants have onsets, compared to ~20% for Controls. By age 19, the FHR group reaches 100% probability of mood disorder onsets, while Controls have just above 50%.

Cox Proportional Hazard Assumptions Test

Before running the primary analysis, we tested whether the proportional hazards assumption was violated. The proportional hazards assumption requires that there be no systematic relationship between covariates and survival time. The test showed that there was no significant relationship between residuals and time for each individual covariate (Figure 8) and the global test for each full model, which confirms that the proportional hazards assumption was not violated (Table 13 – 16).

Functional Connectivity Association with Mood Disorder Onsets

To test how much each covariate contributed to risk of mood disorder onsets, we ran a series of Cox proportional hazards regressions. For the bivariate tests, we found that only

familial risk (hazard ratio=2.33, 95% CI=1.26 – 4.3) and depression symptoms (hazard ratio=1.10, 95% CI=1.01 – 1.2) were prospectively associated with mood disorder onsets (Table 17–26). These findings remained consistent in the multivariate test: Participants in the familial high-risk group had a 2.33 times increased hazard of mood disorder onsets, and each point on the depression symptom scale was associated with 1.1 times increased hazard of mood disorder onset (Table 26). The measures of functional connectivity did not contribute significantly to predicting mood disorder onsets (all p values > 0.05).

Discussion

We investigated whether functional connectivity within and between the DMN and SN is associated with mood disorder onsets in youth at familial risk for major mood disorders. Our results showed that DMN, SN, and DMN-to-SN functional connectivity was not associated with mood disorder onsets. We confirmed previous findings that offspring of parents with major mood disorders had about two-fold increase in probability of mood disorder diagnosis compared to offspring of unaffected parents, and that only family history and subclinical depression symptoms were associated with mood disorder onsets.

There was no significant associations between DMN, SN, or DMN-to-SN connectivity and mood disorder onset in our cohort. Previous research has associated disrupted connectivity – increased SN connectivity, increased DMN connectivity, decreased DMN-to-SN connectivity – in the networks of interest with mood disorders (Mulders et al., 2015b; Sha et al., 2019). Additionally, increased SN has been shown to predict future onset of depression in a familial

high risk group (Pawlak et al., 2022). Inconsistent findings on DMN connectivity in a familial high risk group suggest that it is not clear whether altered DMN connectivity indicates risk for major mood disorders (Piguet et al., 2015; Singh et al., 2014). These previous findings show different results in the DMN connectivity of participants at familial risk compared to those with a mood disorder. Several reasons have been proposed to explain this. First, the discrepancies can be attributed to the heterogeneity in participant characteristics, as well as analytic procedures used by the researchers (Piguet et al., 2015). Second, the DMN might be overcompensating early on, hence the hyperconnectivity in familial risk groups; by the time of illness onset, functional deficits manifest as hypoconnectivity in the DMN (Fornito et al., 2017). Despite the proposed explanations for the discrepancies, caution is needed when interpreting these DMN results. In summary, the current study results do not align with the previous literature, which suggests that DMN, SN, and DMN-to-SN connectivity alterations might not precede major mood disorders. Connectivity disruptions might occur as a consequence of major mood disorders, and can therefore not be a viable risk indicator associated with mood disorder onsets. Future longitudinal studies are needed to replicate or refute these results and help determine the viability of connectivity as a risk factor associated with mood disorder onsets.

From the survival curve analysis, the FHR participants attained 100% probability of a mood disorder onset by the age of 19, while controls only reached upto ~50%. The high probability values in our cohort are likely due to a selection bias since we have a higher rate of attrition for controls compared to familial high-risk participants. Additionally, the fewer participants who remain in the study at later ages tend to have a mood disorder onset. Although the probability values in these results were unrealistically high, the two-fold probability in FHR

versus controls follows closely with what other researchers have reported (Rasic et al., 2014; Weissman et al., 2016).

Consistent with extensive literature, family risk and depressive symptoms were significantly associated with mood disorder onsets (Gershon et al., 1976; Mednick & McNeil, 1968; Rasic et al., 2014). Due to this significant association with mood disorder onsets, clinical risk can complement family history and help in identifying those at risk of developing a mood disorder. Although a power analysis showed that our sample size is adequate to detect significant differences, the fact that we have few mood disorder onsets in our group might be a limitation that future studies can improve on. Additionally, we have a selection bias in our cohort, specifically for the MRI scans; we have a higher rate of attrition of controls compared to familial high-risk participants, and those participants who get scans at later ages tend to have a diagnosis. This bias is a limitation since it drives the probability of mood disorder diagnosis for the scanned participants to the unrealistic levels shown in Figure 7. Future studies where attrition bias is minimized and an evenly balanced sample is used can help provide a more realistic outlook of mood disorder prevalence in the general population.

Conclusion

We found that DMN, SN, and DMN-to-SN connectivity were not prospectively associated with mood disorder onsets. Additionally, we found that participants in the familial risk group are two times more likely to develop mood disorders compared to controls, and that familial risk and depressive symptoms are significantly associated with mood disorder onsets. These findings

indicate that the brain connectivity variables do not complement familial history in prediction of mood disorder onsets. However, clinical risk can complement family history in prediction of mood disorder onsets.

Tables and Figures for Chapter 4

Table 11. Regions used to define the DMN and SN

Regions	Abbreviation	Coordinates (*x, y, z)*
Dorsal medial prefrontal cortex	dmPFC	-7, 46, 35
Posterior cingulate cortex	PCC	0, -52, 30
Dorsal anterior cingulate cortex	dACC	4, 14, 42
Anterior insula	AI	36, 18, 4

Table 12. Demographic and clinical characteristics of participants by family history group

		Controls (n=78)	FHR (n=126)
Sex (Fem/M)		38/40	61/65
Age (years)		13.22 (2.65)	13.38 (2.88)
IQ		109.39 (12.64)	104.45 (14.00)
Depression Score		6.71 (2.46)	7.03 (2.58)
Mood Disorder Diagnosis		6 (Fem = 4)	26 (Fem = 16)
Scans	Initial	78	126
	Follow up	75	168

Note: All quantitative data are expressed as mean ± standard deviation; for sex data, sample size is presented here; due to 6 missing IQ values, the mean and standard deviation presented here are for 121 FHR and 77 Control participants; Follow up scans also includes reliability scans
Abbreviation: FHR, Familial High Risk; Fem, Females; M, Males

Figure 7. Survival Curve in FHR and Control participants

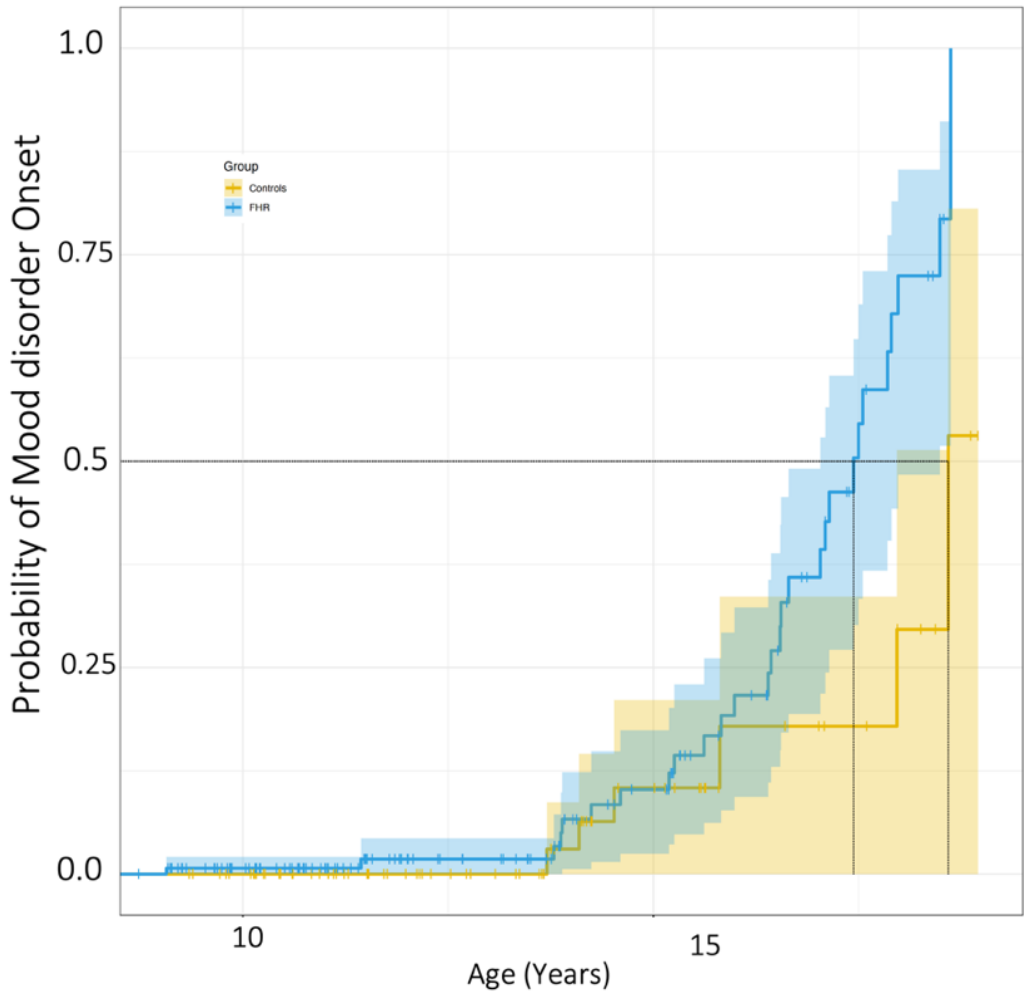


Figure 8. Covariate residuals and their relationship with age

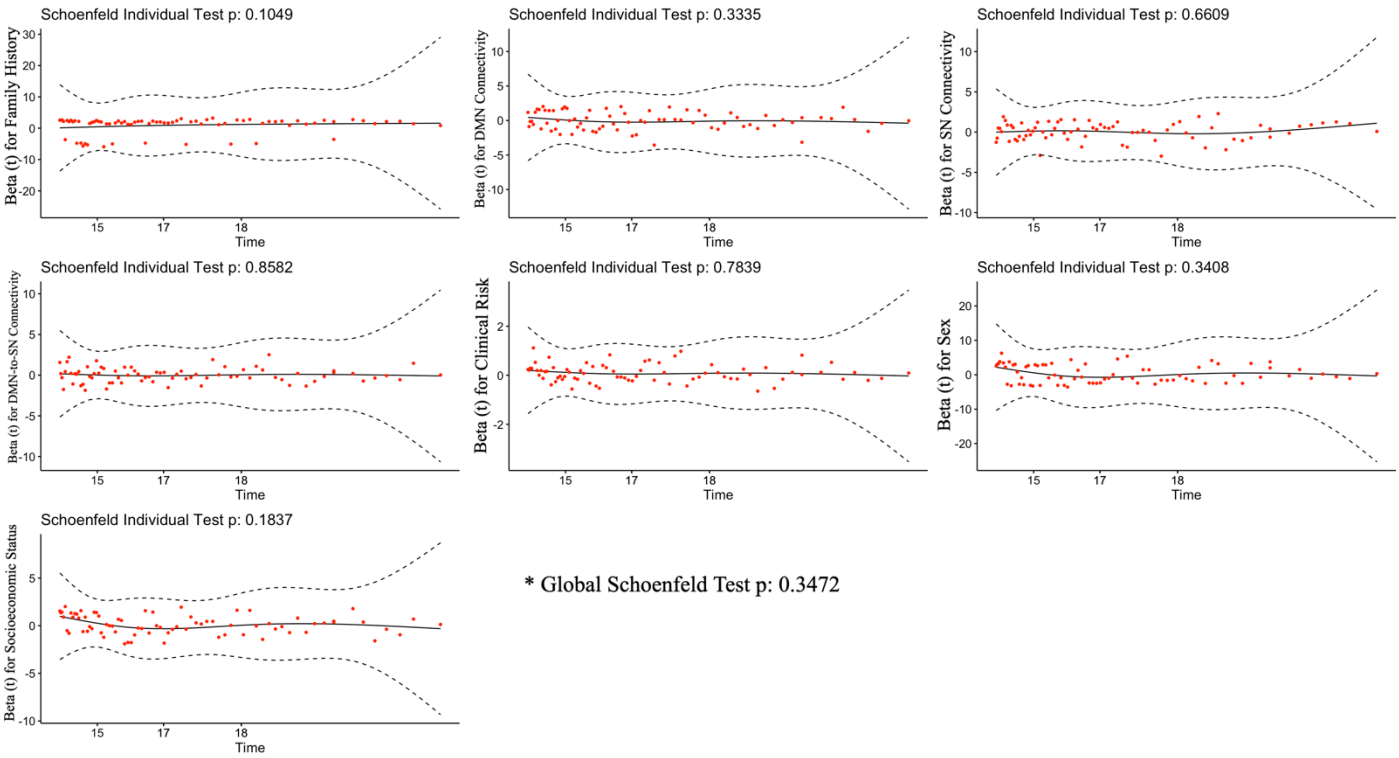


Table 13. Proportional hazards assumption test results (DMN bivariate test)

	DMN Bivariate test		
	Chi-square	**Degrees of freedom**	**P value**
Family History	2.542	1	0.11
DMN	1.173	1	0.28
Depressive symptoms	0.137	1	0.71
SES	1.715	1	0.19
Sex	0.865	1	0.35
Global	8.195	5	0.15

Abbreviation: DMN: Default mode network; SN: Salience network; DMN-to-SN: Default mode network to salience network; SES: Socio-economic status.

Table 14. Proportional hazards assumption test results (SN bivariate test)

	SN Bivariate test		
	Chi-square	**Degrees of freedom**	**P value**
Family History	2.551	1	0.11
SN	0.2391	1	0.62
Depressive symptoms	0.0936	1	0.76
SES	1.522	1	0.22
Sex	0.9230	1	0.34
Global	6.5625	5	0.26

Abbreviation: DMN: Default mode network; SN: Salience network; DMN-to-SN: Default mode network to salience network; SES: Socio-economic status.

Table 15. Proportional hazards assumption test results (DMN-to-SN bivariate test)

	DMN-to-SN Bivariate test		
	Chi-square	**Degrees of freedom**	**P value**
Family History	2.6068	1	0.11
DMN-to-SN	0.006	1	0.94
Depressive symptoms	0.1286	1	0.72
SES	1.67715	1	0.20
Sex	0.9002	1	0.34
Global	6.8891	7	0.23

Abbreviation: DMN: Default mode network; SN: Salience network; DMN-to-SN: Default mode network to salience network; SES: Socio-economic status.

Table 16. Proportional hazards assumption test results (multivariate test)

	Multivariate test		
	Chi-square	**Degrees of freedom**	**P value**
Family History	3.2367	1	0.072
DMN	0.3356	1	0.562
SN	0.6859	1	0.408
DMN-to-SN	0.1460	1	0.702
Depressive symptoms	0.0766	1	0.782
SES	2.3858	1	0.122
Sex	1.2122	1	0.271
Global	9.1019	7	0.245

Abbreviation: DMN: Default mode network; SN: Salience network; DMN-to-SN: Default mode network to salience network; SES: Socio-economic status.

Table 17. Association of DMN connectivity with mood disorder onsets

Predictors	*Estimates*	CI	*p*
DMN Connectivity	1.002	0.785 – 1.277	0.99
Sex	0.985	0.621 – 1.561	0.948
Observations	447		
R^2	0.00		

Table 18. Association of DMN connectivity with mood disorder onsets (accounting for family history)

Predictors	*Estimates*	CI	*p*
DMN Connectivity	0.997	0.776 – 1.281	0.979
Family History	2.125	1.194 – 3.779	**0.010**
Sex	0.979	0.616 – 1.556	0.928
Observations	447		
R^2	0.021		

Table 19. Association of DMN connectivity with mood disorder onsets (accounting for family history, clinical risk, and SES)

Predictors	*Estimates*	CI	*p*
DMN Connectivity	0.955	0.726 – 1.257	0.743
Family History	2.293	1.247 – 4.214	**0.008**
Depression symptoms	1.093	1.013 – 1.179	**0.022**
Socioeconomic status	1.150	0.941 – 1.406	**0.173**
Sex	1.368	0.785 – 2.383	0.269
Observations	405		
R^2	0.038		

Table 20. Association of SN connectivity with mood disorder onsets

Predictors	*Estimates*	CI	*p*
SN Connectivity	1.095	0.879 – 1.365	0.418
Sex	0.971	0.612 – 1.541	0.901
Observations	447		
R^2	0.002		

Table 21. Association of SN connectivity with mood disorder onsets (accounting for family history)

Predictors	***Estimates***	**CI**	***p***
SN Connectivity	1.106	0.890 – 1.374	0.364
Family History	2.142	1.204 – 3.810	**0.010**
Sex	0.963	0.606 – 1.531	0.875
Observations	447		
R^2	0.024		

Table 22. Association of SN connectivity with mood disorder onsets (accounting for family history, clinical risk and SES)

Predictors	***Estimates***	**CI**	***p***
SN Connectivity	1.086	0.859 – 1.374	0.489
Family History	2.311	1.257 – 4.247	**0.007**
Depression symptoms	1.094	1.014 – 1.181	**0.021**
Sex	1.143	0.935 – 1.397	0.191
Observations	405		
R^2	0.039		

Table 23. Association of DMN-to-SN connectivity with mood disorder onsets

Predictors	***Estimates***	**CI**	***p***
DMN-to-SN Connectivity	0.979	0.788 – 1.215	0.846
Sex	0.991	0.623 – 1.574	0.968
Observations	447		
R^2	0.000		

Table 24. Association of DMN-to-SN connectivity with mood disorder onsets (accounting for family history)

Predictors	*Estimates*	CI	*p*
DMN-to-SN Connectivity	0.997	0.800 – 1.243	0.981
Family History	2.124	1.193 – 3.781	**0.010**
Sex	0.979	0.614 – 1.560	0.929
Observations	447		
R^2	0.021		

Table 25. Association of DMN-to-SN connectivity with mood disorder onsets (accounting for family history, clinical risk and SES)

Predictors	*Estimates*	CI	*p*
DMN-to-SN Connectivity	1.019	0.806 – 1.288	0.877
Family History	2.289	1.245 – 4.208	**0.008**
Depression symptoms	1.093	1.011 – 1.181	**0.025**
Socioeconomic status	1.355	0.780 – 2.354	**0.281**
Sex	1.154	0.945 – 1.408	0.160
Observations	405		
R^2	0.037		

Table 26. Multivariate hazard ratio results

Predictors	***Estimates***	**CI**	***p***
Family History	2.328	1.262 – 4.294	**0.007**
DMN Connectivity	0.970	0.735 – 1.281	**0.831**
SN Connectivity	1.082	0.853 – 1.373	**0.515**
DMN-to-SN Connectivity	1.021	0.807 – 1.293	0.861
Depression symptoms	1.096	1.014 – 1.186	**0.021**
Socioeconomic status	1.141	0.935 – 1.397	0.199
Sex	1.356	0.777 – 2.368	0.284
Observations	405		
R^2	0.039		

Chapter 5: Thesis Conclusion

Previous research investigating connectivity in familial high-risk groups had small sample sizes, inconsistent definition of mood disorders, and varying findings. These discrepancies were the motivation for our research looking at brain connectivity in the DMN. We defined a rationale for what familial risk for mood disorders is, selected hub nodes of the DMN where we would see the most activity, and used a large sample size, with the hopes of finding significant differences in DMN connectivity between those at high familial risk versus controls. Additionally, we were interested in studying the relationship between DMN connectivity and depression symptoms. We found that DMN connectivity was similar in the FHR and controls, and that there was no significant relationship between DMN connectivity and depression symptoms. This coincided with some previous research and contradicted a previous paper that had shown increased DMN connectivity in the FHR group. Our findings and the different findings from other groups led us to conclude that there might not be differences in the DMN between the FHR and controls, which would mean that DMN connectivity is not associated with family history for mood disorders.

Upon completing the first project, and further review of the literature, we realized that the salience network was an important network due to its role in coordinating activity between the DMN and other networks, as well as its association with mood disorders. We therefore decided to study the association of these two networks with mood disorder onsets and find out whether they can complement family history and aid in better identification of those at risk of major mood disorder diagnosis. Our analysis showed that connectivity within and between these

networks was not associated with mood disorder onsets, although family history and depressive symptoms were. These results show that connectivity might not be a viable complement to family history, but clinical risk can be used in addition to family history and help in better identification of those at risk. Future research looking at the DMN, SN and other networks implicated in mood disorders (e.g., central executive network, limbic network) can help validate or disprove these findings and help us better understand the association of brain connectivity in mood disorder onsets.

References

Abraham, A., Pedregosa, F., Eickenberg, M., Gervais, P., Mueller, A., Kossaifi, J., Gramfort, A., Thirion, B., & Varoquaux, G. (2014). Machine learning for neuroimaging with scikit-learn. *Frontiers in Neuroinformatics*, *8*. https://www.frontiersin.org/article/10.3389/fninf.2014.00014

Al-Chalabi, A., & Lewis, C. M. (2011). Modelling the Effects of Penetrance and Family Size on Rates of Sporadic and Familial Disease. *Human Heredity*, *71*(4), 281–288. https://doi.org/10.1159/000330167

American Psychiatric Association, & American Psychiatric Association (Eds.). (2013). *Diagnostic and statistical manual of mental disorders: DSM-5* (5th ed). American Psychiatric Association.

Andrews-Hanna, J. R., Reidler, J. S., Sepulcre, J., Poulin, R., & Buckner, R. L. (2010). Functional-Anatomic Fractionation of the Brain's Default Network. *Neuron*, *65*(4), 550–562. https://doi.org/10.1016/j.neuron.2010.02.005

Andrews-Hanna, J. R., Smallwood, J., & Spreng, R. N. (2014). The default network and self-generated thought: Component processes, dynamic control, and clinical relevance. *Annals of the New York Academy of Sciences*, *1316*, 29–52. https://doi.org/10.1111/nyas.12360

Angold, A., Costello, E. J., Messer, S. C., & Pickles, A. (1995). Development of a short questionnaire for use in epidemiological studies of depression in children and adolescents. *International Journal of Methods in Psychiatric Research*, *5*, 237–249.

Angold, A., Erkanli, A., Silberg, J., Eaves, L., & Costello, E. J. (2002). Depression scale scores in 8–17-year-olds: Effects of age and gender. *Journal of Child Psychology and Psychiatry*, *43*(8), 1052–1063. https://doi.org/10.1111/1469-7610.00232

Bakdash, J. Z., & Marusich, L. R. (2017). Repeated Measures Correlation. *Frontiers in Psychology*, *8*. https://www.frontiersin.org/article/10.3389/fpsyg.2017.00456

Barabási, A.-L. (2009). Scale-Free Networks: A Decade and Beyond. *Science*, *325*(5939), 412–413. https://doi.org/10.1126/science.1173299

Berk, M., Hallam, K., Malhi, G. S., Henry, L., Hasty, M., Macneil, C., Yucel, M., Pantelis, C., Murphy, B., Vieta, E., Dodd, S., & McGorry, P. D. (2010). Evidence and implications for early intervention in bipolar disorder. *Journal of Mental Health*, *19*(2), 113–126. https://doi.org/10.3109/09638230903469111

Biswal, B. B., Mennes, M., Zuo, X.-N., Gohel, S., Kelly, C., Smith, S. M., Beckmann, C. F., Adelstein, J. S., Buckner, R. L., Colcombe, S., Dogonowski, A.-M., Ernst, M., Fair, D., Hampson, M., Hoptman, M. J., Hyde, J. S., Kiviniemi, V. J., Kötter, R., Li, S.-J., … Milham, M. P. (2010). Toward discovery science of human brain function. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(10), 4734–4739. https://doi.org/10.1073/pnas.0911855107

Biswal, B., Zerrin Yetkin, F., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar mri. *Magnetic Resonance in Medicine*, *34*(4), 537–541. https://doi.org/10.1002/mrm.1910340409

Broyd, S. J., Demanuele, C., Debener, S., Helps, S. K., James, C. J., & Sonuga-Barke, E. J. S. (2009). Default-mode brain dysfunction in mental disorders: A systematic review.

Neuroscience & Biobehavioral Reviews, *33*(3), 279–296. https://doi.org/10.1016/j.neubiorev.2008.09.002

Buckholtz, J. W., & Meyer-Lindenberg, A. (2012). Psychopathology and the Human Connectome: Toward a Transdiagnostic Model of Risk For Mental Illness. *Neuron*, *74*(6), 990–1004. https://doi.org/10.1016/j.neuron.2012.06.002

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). *The Brain's Default Network*: *Anatomy, Function, and Relevance to Disease*. *Annals of the New York Academy of Sciences*, *1124*(1), 1–38. https://doi.org/10.1196/annals.1440.011

Burton, P. R., Clayton, D. G., Cardon, L. R., Craddock, N., Deloukas, P., Duncanson, A., Kwiatkowski, D. P., McCarthy, M. I., Ouwehand, W. H., Samani, N. J., Todd, J. A., Donnelly, P., Barrett, J. C., Burton, P. R., Davison, D., Donnelly, P., Easton, D., Evans, D., Leung, H.-T., … Primary Investigators. (2007). Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature*, *447*(7145), Article 7145. https://doi.org/10.1038/nature05911

Chai, X. J., Hirshfeld-Becker, D., Biederman, J., Uchida, M., Doehrmann, O., Leonard, J. A., Salvatore, J., Kenworthy, T., Brown, A., Kagan, E., de los Angeles, C., Gabrieli, J. D. E., & Whitfield-Gabrieli, S. (2016). Altered Intrinsic Functional Brain Architecture in Children at Familial Risk of Major Depression. *Biological Psychiatry*, *80*(11), 849–858. https://doi.org/10.1016/j.biopsych.2015.12.003

Chase, H. W., Auerbach, R. P., Brent, D. A., Posner, J., Weissman, M. M., & Talati, A. (2021). Dissociating default mode network resting state markers of suicide from familial risk factors for depression. *Neuropsychopharmacology*, *46*(10), Article 10. https://doi.org/10.1038/s41386-021-01022-5

Clark, E., Munday, J., & Watts, A. (2022). Stigma, shame and family secrets as consequences of mental illness in previous generations: A micro-history approach. *Health*, 13634593221114752. https://doi.org/10.1177/13634593221114751

Dai, L., Zhou, H., Xu, X., & Zuo, Z. (2019). Brain structural and functional changes in patients with major depressive disorder: A literature review. *PeerJ*, *7*, e8170. https://doi.org/10.7717/peerj.8170

Dosenbach, N. U. F., Fair, D. A., Miezin, F. M., Cohen, A. L., Wenger, K. K., Dosenbach, R. A. T., Fox, M. D., Snyder, A. Z., Vincent, J. L., Raichle, M. E., Schlaggar, B. L., & Petersen, S. E. (2007). Distinct brain networks for adaptive and stable task control in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(26), 11073–11078. https://doi.org/10.1073/pnas.0704320104

Drobinin, V., Van Gestel, H., Helmick, C. A., Schmidt, M. H., Bowen, C. V., & Uher, R. (2020). Reliability of multimodal MRI brain measures in youth at risk for mental illness. *Brain and Behavior*, *10*(6). https://doi.org/10.1002/brb3.1609

Drobinin, V., Van Gestel, H., Helmick, C. A., Schmidt, M. H., Bowen, C. V., & Uher, R. (2021). The Developmental Brain Age Is Associated With Adversity, Depression, and Functional Outcomes Among Adolescents. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, S2451902221002561. https://doi.org/10.1016/j.bpsc.2021.09.004

Duffy, A., Alda, M., Hajek, T., Sherry, S. B., & Grof, P. (2010). Early stages in the development of bipolar disorder. *Journal of Affective Disorders*, *121*(1), 127–135. https://doi.org/10.1016/j.jad.2009.05.022

Durdurak, B. B., Altaweel, N., Upthegrove, R., & Marwaha, S. (2022). Understanding the development of bipolar disorder and borderline personality disorder in young people: A

meta-review of systematic reviews. *Psychological Medicine*, *52*(16), 1–14. https://doi.org/10.1017/S0033291722003002

Eaton, N. R., Keyes, K. M., Krueger, R. F., Balsis, S., Skodol, A. E., Markon, K. E., Grant, B. F., & Hasin, D. S. (2012). An invariant dimensional liability model of gender differences in mental disorder prevalence: Evidence from a national sample. *Journal of Abnormal Psychology*, *121*, 282–288. https://doi.org/10.1037/a0024780

Faedda, G. L., Marangoni, C., Serra, G., Salvatore, P., Sani, G., Vázquez, G. H., Tondo, L., Girardi, P., Baldessarini, R. J., & Koukopoulos†, A. (2015). Precursors of Bipolar Disorders: A Systematic Literature Review of Prospective Studies. *The Journal of Clinical Psychiatry*, *76*(5), 14973. https://doi.org/10.4088/JCP.13r08900

Finn, E. S., Shen, X., Scheinost, D., Rosenberg, M. D., Huang, J., Chun, M. M., Papademetris, X., & Constable, R. T. (2015). Functional connectome fingerprinting: Identifying individuals using patterns of brain connectivity. *Nature Neuroscience*, *18*(11), Article 11. https://doi.org/10.1038/nn.4135

Fornito, A., Bullmore, E. T., & Zalesky, A. (2017). Opportunities and Challenges for Psychiatry in the Connectomic Era. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *2*(1), 9–19. https://doi.org/10.1016/j.bpsc.2016.08.003

Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience*, *8*(9), 700–711. https://doi.org/10.1038/nrn2201

Friston, K. J. (2011). Functional and Effective Connectivity: A Review. *Brain Connectivity*, *1*(1), 13–36. https://doi.org/10.1089/brain.2011.0008

Gershon, E. S., Bunney, W. E., Leckman, J. F., Van Eerdewegh, M., & DeBauche, B. A. (1976). The inheritance of affective disorders: A review of data and of hypotheses. *Behavior Genetics*, *6*(3), 227–261. https://doi.org/10.1007/BF01065722

Ghaznavi, S., Chou, T., Dougherty, D. D., & Nierenberg, A. A. (2023). Differential patterns of default mode network activity associated with negative and positive rumination in bipolar disorder. *Journal of Affective Disorders*, *323*, 607–616. https://doi.org/10.1016/j.jad.2022.12.014

Goldstein-Piekarski, A. N., Ball, T. M., Samara, Z., Staveland, B. R., Keller, A. S., Fleming, S. L., Grisanzio, K. A., Holt-Gosselin, B., Stetz, P., Ma, J., & Williams, L. M. (2022). Mapping Neural Circuit Biotypes to Symptoms and Behavioral Dimensions of Depression and Anxiety. *Biological Psychiatry*, *91*(6), 561–571. https://doi.org/10.1016/j.biopsych.2021.06.024

Gong, J., Chen, G., Jia, Y., Zhong, S., Zhao, L., Luo, X., Qiu, S., Lai, S., Qi, Z., Huang, L., & Wang, Y. (2019). Disrupted functional connectivity within the default mode network and salience network in unmedicated bipolar II disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *88*, 11–18. https://doi.org/10.1016/j.pnpbp.2018.06.012

Gong, Q., & He, Y. (2015). Depression, Neuroimaging and Connectomics: A Selective Overview. *Biological Psychiatry*, *77*(3), 223–235. https://doi.org/10.1016/j.biopsych.2014.08.009

Goodkind, M., Eickhoff, S. B., Oathes, D. J., Jiang, Y., Chang, A., Jones-Hagata, L. B., Ortega, B. N., Zaiko, Y. V., Roach, E. L., Korgaonkar, M. S., Grieve, S. M., Galatzer-Levy, I., Fox, P. T., & Etkin, A. (2015). Identification of a Common Neurobiological Substrate for

Mental Illness. *JAMA Psychiatry*, *72*(4), 305–315. https://doi.org/10.1001/jamapsychiatry.2014.2206

Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(1), 253–258. Scopus. https://doi.org/10.1073/pnas.0135058100

Gusnard, D. A., & Raichle, M. E. (2001). Searching for a baseline: Functional imaging and the resting human brain. *Nature Reviews Neuroscience*, *2*(10), Article 10. https://doi.org/10.1038/35094500

Heinze, K., Shen, X., Hawkins, E., Harris, M. A., de Nooij, L., McIntosh, A. M., Wood, S. J., & Whalley, H. C. (2020). Aberrant structural covariance networks in youth at high familial risk for mood disorder. *Bipolar Disorders*, *22*(2), 155–162. https://doi.org/10.1111/bdi.12868

Herrman, H., Patel, V., Kieling, C., Berk, M., Buchweitz, C., Cuijpers, P., Furukawa, T. A., Kessler, R. C., Kohrt, B. A., Maj, M., McGorry, P., Reynolds, C. F., Weissman, M. M., Chibanda, D., Dowrick, C., Howard, L. M., Hoven, C. W., Knapp, M., Mayberg, H. S., … Wolpert, M. (2022). Time for united action on depression: A Lancet-World Psychiatric Association Commission. *Lancet (London, England)*, *399*(10328), 957–1022. https://doi.org/10.1016/S0140-6736(21)02141-3

Hirschfeld, R. M. (2014). Differential diagnosis of bipolar disorder and major depressive disorder. *Journal of Affective Disorders*, *169*, S12–S16. https://doi.org/10.1016/S0165-0327(14)70004-7

Jobson, D. D., Hase, Y., Clarkson, A. N., & Kalaria, R. N. (2021). The role of the medial prefrontal cortex in cognition, ageing and dementia. *Brain Communications*, *3*(3), fcab125. https://doi.org/10.1093/braincomms/fcab125

Judd, L. L., Akiskal, H. S., Schettler, P. J., Coryell, W., Endicott, J., Maser, J. D., Solomon, D. A., Leon, A. C., & Keller, M. B. (2003). A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. *Archives of General Psychiatry*, *60*(3), 261–269. https://doi.org/10.1001/archpsyc.60.3.261

Judd, L. L., Akiskal, H. S., Schettler, P. J., Endicott, J., Maser, J., Solomon, D. A., Leon, A. C., Rice, J. A., & Keller, M. B. (2002). The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Archives of General Psychiatry*, *59*(6), 530–537. https://doi.org/10.1001/archpsyc.59.6.530

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., Williamson, D., & Ryan, N. (1997). Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): Initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry*, *36*(7), 980–988. https://doi.org/10.1097/00004583-199707000-00021

Kim-Cohen, J., Caspi, A., Moffitt, T. E., Harrington, H., Milne, B. J., & Poulton, R. (2003). Prior Juvenile Diagnoses in Adults With Mental Disorder: Developmental Follow-Back of a Prospective-Longitudinal Cohort. *Archives of General Psychiatry*, *60*(7), 709–717. https://doi.org/10.1001/archpsyc.60.7.709

Lund, M. J., Alnæs, D., de Lange, A.-M. G., Andreassen, O. A., Westlye, L. T., & Kaufmann, T. (2021). Brain age prediction using fMRI network coupling in youths and associations

with psychiatric symptoms. *NeuroImage : Clinical*, *33*, 102921. https://doi.org/10.1016/j.nicl.2021.102921

MacKenzie, L. E., Patterson, V. C., Zwicker, A., Drobinin, V., Fisher, H. L., Abidi, S., Greve, A. N., Bagnell, A., Propper, L., Alda, M., Pavlova, B., & Uher, R. (2017). Hot and cold executive functions in youth with psychotic symptoms. *Psychological Medicine*, *47*(16), 2844–2853. https://doi.org/10.1017/S0033291717001374

McGorry, P. (2013). Early Clinical Phenotypes and Risk for Serious Mental Disorders in Young People: Need for Care Precedes Traditional Diagnoses in Mood and Psychotic Disorders. *The Canadian Journal of Psychiatry*, *58*(1), 19–21. https://doi.org/10.1177/070674371305800105

McGorry, P. D., Nelson, B., Goldstone, S., & Yung, A. R. (2010). Clinical Staging: A Heuristic and Practical Strategy for New Research and Better Health and Social Outcomes for Psychotic and Related Mood Disorders. *The Canadian Journal of Psychiatry*, *55*(8), 486–497. https://doi.org/10.1177/070674371005500803

McGuffin, P., Rijsdijk, F., Andrew, M., Sham, P., Katz, R., & Cardno, A. (2003). The Heritability of Bipolar Affective Disorder and the Genetic Relationship to Unipolar Depression. *Archives of General Psychiatry*, *60*(5), 497. https://doi.org/10.1001/archpsyc.60.5.497

Mednick, S. A., & McNeil, T. F. (1968). Current methodology in research on the etiology of schizophrenia: Serious difficulties which suggest the use of the high-risk-group method. *Psychological Bulletin*, *70*, 681–693. https://doi.org/10.1037/h0026836

Meier, S. M., Pavlova, B., Dalsgaard, S., Nordentoft, M., Mors, O., Mortensen, P. B., & Uher, R. (2018). Attention-deficit hyperactivity disorder and anxiety disorders as precursors of

bipolar disorder onset in adulthood. *The British Journal of Psychiatry*, *213*(3), 555–560. https://doi.org/10.1192/bjp.2018.111

Menon, V. (2011). Large-scale brain networks and psychopathology: A unifying triple network model. *Trends in Cognitive Sciences*, *15*(10), 483–506. https://doi.org/10.1016/j.tics.2011.08.003

Menon, V. (2015). Salience Network. In *Brain Mapping* (pp. 597–611). Elsevier. https://doi.org/10.1016/B978-0-12-397025-1.00052-X

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: A network model of insula function. *Brain Structure & Function*, *214*(5–6), 655–667. https://doi.org/10.1007/s00429-010-0262-0

Mulders, P. C., van Eijndhoven, P. F., Schene, A. H., Beckmann, C. F., & Tendolkar, I. (2015a). Resting-state functional connectivity in major depressive disorder: A review. *Neuroscience & Biobehavioral Reviews*, *56*, 330–344. https://doi.org/10.1016/j.neubiorev.2015.07.014

Mulders, P. C., van Eijndhoven, P. F., Schene, A. H., Beckmann, C. F., & Tendolkar, I. (2015b). Resting-state functional connectivity in major depressive disorder: A review. *Neuroscience & Biobehavioral Reviews*, *56*, 330–344. https://doi.org/10.1016/j.neubiorev.2015.07.014

Nazarova, A., Schmidt, M., Cookey, J., & Uher, R. (2022). Neural markers of familial risk for depression – A systematic review. *Developmental Cognitive Neuroscience*, *58*, 101161. https://doi.org/10.1016/j.dcn.2022.101161

Noble, S., Scheinost, D., & Constable, R. T. (2019). A decade of test-retest reliability of functional connectivity: A systematic review and meta-analysis. *NeuroImage*, *203*, 116157. https://doi.org/10.1016/j.neuroimage.2019.116157

Öngür, D., Lundy, M., Greenhouse, I., Shinn, A. K., Menon, V., Cohen, B. M., & Renshaw, P. F. (2010). Default mode network abnormalities in bipolar disorder and schizophrenia. *Psychiatry Research: Neuroimaging*, *183*(1), 59–68. https://doi.org/10.1016/j.pscychresns.2010.04.008

Padgaonkar, N. T., Lawrence, K. E., Hernandez, L. M., Green, S. A., Galván, A., & Dapretto, M. (2020). Sex Differences in Internalizing Symptoms and Amygdala Functional Connectivity in Neurotypical Youth. *Developmental Cognitive Neuroscience*, *44*, 100797. https://doi.org/10.1016/j.dcn.2020.100797

Palaniyappan, L., Deshpande, G., Lanka, P., Rangaprakash, D., Iwabuchi, S., Francis, S., & Liddle, P. F. (2019). Effective connectivity within a triple network brain system discriminates schizophrenia spectrum disorders from psychotic bipolar disorder at the single-subject level. *Schizophrenia Research*, *214*, 24–33. https://doi.org/10.1016/j.schres.2018.01.006

Pannekoek, J. N., van der Werff, S. j. a., Meens, P. H. F., van den Bulk, B. G., Jolles, D. D., Veer, I. M., van Lang, N. D. J., Rombouts, S. A. R. B., van der Wee, N. J. A., & Vermeiren, R. R. J. M. (2014). Aberrant resting-state functional connectivity in limbic and salience networks in treatment-naïve clinically depressed adolescents. *Journal of Child Psychology and Psychiatry*, *55*(12), 1317–1327. https://doi.org/10.1111/jcpp.12266

Patterson, V. C., Pencer, A., Pavlova, B., Awadia, A., MacKenzie, L. E., Zwicker, A., Drobinin, V., Howes Vallis, E., & Uher, R. (2021). Youth Experience Tracker Instrument: A self-

report measure of developmental antecedents to severe mental illness. *Early Intervention in Psychiatry*, *15*(3), 676–685. https://doi.org/10.1111/eip.13007

Pawlak, M., Bray, S., & Kopala-Sibley, D. C. (2022). Resting state functional connectivity as a marker of internalizing disorder onset in high-risk youth. *Scientific Reports*, *12*(1), Article 1. https://doi.org/10.1038/s41598-022-25805-y

Piguet, C., Fodoulian, L., Aubry, J.-M., Vuilleumier, P., & Houenou, J. (2015). Bipolar disorder: Functional neuroimaging markers in relatives. *Neuroscience & Biobehavioral Reviews*, *57*, 284–296. https://doi.org/10.1016/j.neubiorev.2015.08.015

Pine, D. S., Cohen, E., Cohen, P., & Brook, J. (1999). Adolescent Depressive Symptoms as Predictors of Adult Depression: Moodiness or Mood Disorder? *American Journal of Psychiatry*, *156*(1), 133–135. https://doi.org/10.1176/ajp.156.1.133

Pine, D. S., & Fox, N. A. (2015). Childhood Antecedents and Risk for Adult Mental Disorders. *Annual Review of Psychology*, *66*(1), 459–485. https://doi.org/10.1146/annurev-psych-010814-015038

Posner, J., Cha, J., Wang, Z., Talati, A., Warner, V., Gerber, A., Peterson, B. S., & Weissman, M. (2016). Increased Default Mode Network Connectivity in Individuals at High Familial Risk for Depression. *Neuropsychopharmacology*, *41*(7), 1759–1767. https://doi.org/10.1038/npp.2015.342

Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2012a). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage*, *59*(3), 2142–2154. https://doi.org/10.1016/j.neuroimage.2011.10.018

Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2012b). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *NeuroImage*, *59*(3), 2142–2154. https://doi.org/10.1016/j.neuroimage.2011.10.018

Power, J. D., Cohen, A. L., Nelson, S. M., Wig, G. S., Barnes, K. A., Church, J. A., Vogel, A. C., Laumann, T. O., Miezin, F. M., Schlaggar, B. L., & Petersen, S. E. (2011). Functional network organization of the human brain. *Neuron*, *72*(4), 665–678. https://doi.org/10.1016/j.neuron.2011.09.006

Power, J. D., Mitra, A., Laumann, T. O., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2014). Methods to detect, characterize, and remove motion artifact in resting state fMRI. *NeuroImage*, *84*, 10.1016/j.neuroimage.2013.08.048. https://doi.org/10.1016/j.neuroimage.2013.08.048

Price, J. L., & Drevets, W. C. (2012). Neural circuits underlying the pathophysiology of mood disorders. *Trends in Cognitive Sciences*, *16*(1), 61–71. https://doi.org/10.1016/j.tics.2011.12.011

Qu, Y., Rappaport, B. I., Luby, J. L., & Barch, D. M. (2021). No associations in preregistered study of youth depression and functional connectivity of fronto-parietal and default mode networks. *Neuroimage: Reports*, *1*(3), 100036. https://doi.org/10.1016/j.ynirp.2021.100036

Raichle, M. E. (2015). The Brain's Default Mode Network. *Annual Review of Neuroscience*, *38*(1), 433–447. https://doi.org/10.1146/annurev-neuro-071013-014030

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of*

Sciences of the United States of America, *98*(2), 676–682. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC14647/

Rasic, D., Hajek, T., Alda, M., & Uher, R. (2014). Risk of Mental Illness in Offspring of Parents With Schizophrenia, Bipolar Disorder, and Major Depressive Disorder: A Meta-Analysis of Family High-Risk Studies. *Schizophrenia Bulletin*, *40*(1), 28–38. https://doi.org/10.1093/schbul/sbt114

Rice, F., Sellers, R., Hammerton, G., Eyre, O., Bevan-Jones, R., Thapar, A. K., Collishaw, S., Harold, G. T., & Thapar, A. (2017). Antecedents of New-Onset Major Depressive Disorder in Children and Adolescents at High Familial Risk. *JAMA Psychiatry*, *74*(2), 153. https://doi.org/10.1001/jamapsychiatry.2016.3140

Sanders, A. F. P., Harms, M. P., Kandala, S., Marek, S., Somerville, L. H., Bookheimer, S. Y., Dapretto, M., Thomas, K. M., Van Essen, D. C., Yacoub, E., & Barch, D. M. (2023). Age-related differences in resting-state functional connectivity from childhood to adolescence. *Cerebral Cortex*, bhad011. https://doi.org/10.1093/cercor/bhad011

Satterthwaite, T. D., Elliott, M. A., Gerraty, R. T., Ruparel, K., Loughead, J., Calkins, M. E., Eickhoff, S. B., Hakonarson, H., Gur, R. C., Gur, R. E., & Wolf, D. H. (2013). An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state functional connectivity data. *NeuroImage*, *64*, 240–256. https://doi.org/10.1016/j.neuroimage.2012.08.052

Scalabrini, A., Vai, B., Poletti, S., Damiani, S., Mucci, C., Colombo, C., Zanardi, R., Benedetti, F., & Northoff, G. (2020). All roads lead to the default-mode network-global source of DMN abnormalities in major depressive disorder. *Neuropsychopharmacology: Official*

Publication of the American College of Neuropsychopharmacology, *45*(12), 2058–2069. https://doi.org/10.1038/s41386-020-0785-x

Seeley, W. W. (2019). The Salience Network: A Neural System for Perceiving and Responding to Homeostatic Demands. *Journal of Neuroscience*, *39*(50), 9878–9882. https://doi.org/10.1523/JNEUROSCI.1138-17.2019

Sha, Z., Wager, T. D., Mechelli, A., & He, Y. (2019). Common Dysfunction of Large-Scale Neurocognitive Networks Across Psychiatric Disorders. *Biological Psychiatry*, *85*(5), 379–388. https://doi.org/10.1016/j.biopsych.2018.11.011

Shapero, B. G., Chai, X. J., Vangel, M., Biederman, J., Hoover, C. S., Whitfield-Gabrieli, S., Gabrieli, J. D. E., & Hirshfeld-Becker, D. R. (2019). Neural Markers of Depression Risk Predict the Onset of Depression. *Psychiatry Research. Neuroimaging*, *285*, 31–39. https://doi.org/10.1016/j.pscychresns.2019.01.006

Sharma, A., Wolf, D. H., Ciric, R., Kable, J. W., Moore, T. M., Vandekar, S. N., Katchmar, N., Daldal, A., Ruparel, K., Davatzikos, C., Elliott, M. A., Calkins, M. E., Shinohara, R. T., Bassett, D. S., & Satterthwaite, T. D. (2017). Common Dimensional Reward Deficits Across Mood and Psychotic Disorders: A Connectome-Wide Association Study. *American Journal of Psychiatry*, *174*(7), 657–666. https://doi.org/10.1176/appi.ajp.2016.16070774

Shulman, G. L., Fiez, J. A., Corbetta, M., Buckner, R. L., Miezin, F. M., Raichle, M. E., & Petersen, S. E. (1997). Common Blood Flow Changes across Visual Tasks: II. Decreases in Cerebral Cortex. *Journal of Cognitive Neuroscience*, *9*(5), 648–663. https://doi.org/10.1162/jocn.1997.9.5.648

Singh, M. K., Chang, K. D., Kelley, R. G., Saggar, M., Reiss, A. L., & Gotlib, I. H. (2014). Early signs of anomalous neural functional connectivity in healthy offspring of parents with bipolar disorder. *Bipolar Disorders*, *16*(7), 678–689. https://doi.org/10.1111/bdi.12221

Spitzer, R. L., Williams, J. B., Gibbon, M., & First, M. B. (1992). The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. *Archives of General Psychiatry*, *49*(8), 624–629. https://doi.org/10.1001/archpsyc.1992.01820080032005

Sripada, R. K., Swain, J. E., Evans, G. W., Welsh, R. C., & Liberzon, I. (2014). Childhood Poverty and Stress Reactivity Are Associated with Aberrant Functional Connectivity in Default Mode Network. *Neuropsychopharmacology*, *39*(9), 2244. https://doi.org/10.1038/npp.2014.75

Stevens, M. C. (2016). The contributions of resting state and task-based functional connectivity studies to our understanding of adolescent brain network maturation. *Neuroscience & Biobehavioral Reviews*, *70*, 13–32. https://doi.org/10.1016/j.neubiorev.2016.07.027

Tahmasian, M., Knight, D. C., Manoliu, A., Schwerthöffer, D., Scherr, M., Meng, C., Shao, J., Peters, H., Doll, A., Khazaie, H., Drzezga, A., Bäuml, J., Zimmer, C., Förstl, H., Wohlschläger, A. M., Riedl, V., & Sorg, C. (2013). Aberrant Intrinsic Connectivity of Hippocampus and Amygdala Overlap in the Fronto-Insular and Dorsomedial-Prefrontal Cortex in Major Depressive Disorder. *Frontiers in Human Neuroscience*, *7*, 639. https://doi.org/10.3389/fnhum.2013.00639

Teeuw, J., Brouwer, R. M., Guimarães, J. P. O. F. T., Brandner, P., Koenis, M. M. G., Swagerman, S. C., Verwoert, M., Boomsma, D. I., & Hulshoff Pol, H. E. (2019). Genetic and environmental influences on functional connectivity within and between canonical

cortical resting-state networks throughout adolescent development in boys and girls. *NeuroImage*, *202*, 116073. https://doi.org/10.1016/j.neuroimage.2019.116073

Uddin, L. Q. (2015). Salience processing and insular cortical function and dysfunction. *Nature Reviews Neuroscience*, *16*(1), Article 1. https://doi.org/10.1038/nrn3857

Uher, R., Cumby, J., MacKenzie, L. E., Morash-Conway, J., Glover, J. M., Aylott, A., Propper, L., Abidi, S., Bagnell, A., Pavlova, B., Hajek, T., Lovas, D., Pajer, K., Gardner, W., Levy, A., & Alda, M. (2014). A familial risk enriched cohort as a platform for testing early interventions to prevent severe mental illness. *BMC Psychiatry*, *14*(1), 344. https://doi.org/10.1186/s12888-014-0344-2

Van Dijk, K. R. A., Sabuncu, M. R., & Buckner, R. L. (2012). The Influence of Head Motion on Intrinsic Functional Connectivity MRI. *NeuroImage*, *59*(1), 431–438. https://doi.org/10.1016/j.neuroimage.2011.07.044

Van Essen, D. C., Smith, S. M., Barch, D. M., Behrens, T. E. J., Yacoub, E., & Ugurbil, K. (2013). The WU-Minn Human Connectome Project: An overview. *NeuroImage*, *80*, 62–79. https://doi.org/10.1016/j.neuroimage.2013.05.041

van Lang, N. D. J., Ferdinand, R. F., & Verhulst, F. C. (2007). Predictors of future depression in early and late adolescence. *Journal of Affective Disorders*, *97*(1–3), 137–144. https://doi.org/10.1016/j.jad.2006.06.007

van Oort, E. S. B., van Cappellen van Walsum, A. M., & Norris, D. G. (2014). An investigation into the functional and structural connectivity of the Default Mode Network. *NeuroImage*, *90*, 381–389. https://doi.org/10.1016/j.neuroimage.2013.12.051

Weissman, M. M., Wickramaratne, P., Gameroff, M. J., Warner, V., Pilowsky, D., Kohad, R. G., Verdeli, H., Skipper, J., & Talati, A. (2016). Offspring of Depressed Parents: 30 Years

Later. *The American Journal of Psychiatry*, *173*(10), 1024–1032. https://doi.org/10.1176/appi.ajp.2016.15101327

Whitfield-Gabrieli, S., & Ford, J. M. (2012a). Default Mode Network Activity and Connectivity in Psychopathology. *Annual Review of Clinical Psychology*, *8*(1), 49–76. https://doi.org/10.1146/annurev-clinpsy-032511-143049

Whitfield-Gabrieli, S., & Ford, J. M. (2012b). Default Mode Network Activity and Connectivity in Psychopathology. *Annual Review of Clinical Psychology*, *8*(1), 49–76. https://doi.org/10.1146/annurev-clinpsy-032511-143049

Woodward, N. D., & Cascio, C. J. (2015). Resting-State Functional Connectivity in Psychiatric Disorders. *JAMA Psychiatry*, *72*(8), 743. https://doi.org/10.1001/jamapsychiatry.2015.0484

Wray, N. R., Ripke, S., Mattheisen, M., Trzaskowski, M., Byrne, E. M., Abdellaoui, A., Adams, M. J., Agerbo, E., Air, T. M., Andlauer, T. F. M., Bacanu, S.-A., Bækvad-Hansen, M., Beekman, A. T. F., Bigdeli, T. B., Binder, E. B., Blackwood, D. H. R., Bryois, J., Buttenschøn, H. N., Bybjerg-Grauholm, J., … Sullivan, P. F. (2018). Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nature Genetics*, *50*(5), 668–681. https://doi.org/10.1038/s41588-018-0090-3

Yan, C.-G., Chen, X., Li, L., Castellanos, F. X., Bai, T.-J., Bo, Q.-J., Cao, J., Chen, G.-M., Chen, N.-X., Chen, W., Cheng, C., Cheng, Y.-Q., Cui, X.-L., Duan, J., Fang, Y.-R., Gong, Q.-Y., Guo, W.-B., Hou, Z.-H., Hu, L., … Zang, Y.-F. (2019). Reduced default mode network functional connectivity in patients with recurrent major depressive disorder. *Proceedings of the National Academy of Sciences*, *116*(18), 9078–9083. https://doi.org/10.1073/pnas.1900390116

Yoon, S., Kim, T. D., Kim, J., & Lyoo, I. K. (2020). Altered functional activity in bipolar disorder: A comprehensive review from a large-scale network perspective. *Brain and Behavior*, *11*(1), e01953. https://doi.org/10.1002/brb3.1953

Yu, F., Fang, H., Zhang, J., Wang, Z., Ai, H., Kwok, V. P. Y., Fang, Y., Guo, Y., Wang, X., Zhu, C., Luo, Y., Xu, P., & Wang, K. (2022). Individualized prediction of consummatory anhedonia from functional connectome in major depressive disorder. *Depression and Anxiety*, *39*(12), 858–869. https://doi.org/10.1002/da.23292

Zhang, S., Zhou, J., Cui, J., Zhang, Z., Liu, R., Feng, Y., Feng, L., Wang, Y., Chen, X., Wu, H., Jin, Y., Zhou, Y., & Wang, G. (n.d.). Effects of 12-week escitalopram treatment on resting-state functional connectivity of large-scale brain networks in major depressive disorder. *Human Brain Mapping*, *n/a*(n/a). https://doi.org/10.1002/hbm.26231

Zhao, Q., Swati, Z. N. K., Metmer, H., Sang, X., & Lu, J. (2019). Investigating executive control network and default mode network dysfunction in major depressive disorder. *Neuroscience Letters*, *701*, 154–161. https://doi.org/10.1016/j.neulet.2019.02.045

Zheng, R., Chen, Y., Jiang, Y., Zhou, B., Li, S., Wei, Y., Wang, C., Han, S., Zhang, Y., & Cheng, J. (2022). Abnormal dynamic functional connectivity in first-episode, drug-naïve adolescents with major depressive disorder. *Journal of Neuroscience Research*, *100*(7), 1463–1475. https://doi.org/10.1002/jnr.25047

Zhu, X., Zhu, Q., Shen, H., Liao, W., & Yuan, F. (2017). Rumination and Default Mode Network Subsystems Connectivity in First-episode, Drug-Naive Young Patients with Major Depressive Disorder. *Scientific Reports*, *7*, 43105. https://doi.org/10.1038/srep43105

Zovetti, N., Rossetti, M. G., Perlini, C., Maggioni, E., Bontempi, P., Bellani, M., & Brambilla, P. (2020). Default mode network activity in bipolar disorder. *Epidemiology and Psychiatric Sciences*, *29*, e166. https://doi.org/10.1017/S2045796020000803

Zwicker, A., Drobinin, V., MacKenzie, L. E., Howes Vallis, E., Patterson, V. C., Cumby, J., Propper, L., Abidi, S., Bagnell, A., Pavlova, B., Alda, M., & Uher, R. (2020). Affective lability in offspring of parents with major depressive disorder, bipolar disorder and schizophrenia. *European Child & Adolescent Psychiatry*, *29*(4), 445–451. https://doi.org/10.1007/s00787-019-01355-z

Therneau, T. (2020). coxme: Mixed effects Cox models. R package version 2.2-18-1. Vienna, Austria: *R Foundation for Statistical Computing*.

Kassambara A, Kosinski M, Biecek P: survminer: Drawing survival curves using "ggplot2." 2021. https://cran.r-project.org/package5 survminer

Therneau TM: survival: A package for survival analysis in R. 2020. https://cran.r-project.org/package5survival

APPENDIX A: YOUTH EXPERIENCE TRACKER INSTRUMENT (YETI)

Figure 9. YETI questionnaire (depression items highlighted)

How has your week been?

Tick one box for each question that best describes how you have been over the past 7 days.

	Never	*Once or twice*	*Often*	*All the time or Every day*
I felt nervous around people I don't know well.	☐	☐	☐	☐
I felt miserable or unhappy.	☐	☐	☐	☐
I lost my temper.	☐	☐	☐	☐
I didn't enjoy anything at all.	☐	☐	☐	☐
All of a sudden I felt really scared for no reason at all.	☐	☐	☐	☐
I suddenly became nervous and fidgety.	☐	☐	☐	☐
I worried about the future.	☐	☐	☐	☐
I was angry.	☐	☐	☐	☐
I felt too tired to do anything.	☐	☐	☐	☐
I worried about going to school or work.	☐	☐	☐	☐
I had bursts of silliness.	☐	☐	☐	☐
I felt I was a bad person.	☐	☐	☐	☐
I worried about not being as good as others.	☐	☐	☐	☐
I thought nobody really loved me.	☐	☐	☐	☐
I got easily annoyed by others.	☐	☐	☐	☐
I had difficulty falling asleep.	☐	☐	☐	☐
I woke up during the night and could not get back to sleep.	☐	☐	☐	☐
I suddenly became sad for no apparent reason.	☐	☐	☐	☐
I heard voices or noises that other people could not hear.	☐	☐	☐	☐
I saw something or someone that other people could not see.	☐	☐	☐	☐
I thought I was being followed or spied on.	☐	☐	☐	☐
Someone knew what I was thinking even though I did not tell them.	☐	☐	☐	☐
I felt like the world around me was not real.	☐	☐	☐	☐
I could not express myself as clearly as before.	☐	☐	☐	☐
I could not understand words or conversations that I could easily understand before.	☐	☐	☐	☐
Things looked differently than they usually do.	☐	☐	☐	☐

Is there anything else you would like to tell us of your experiences in the past week? If yes, please write it into the box below.

Thank you!

APPENDIX B: FMRI PREPROCESSING RESULTS

fMRIPrep results included in this manuscript come from preprocessing performed using fMRIPrep 20.2.1 (Esteban, Markiewicz, et al. (2018); Esteban, Blair, et al. (2018); RRID:SCR_016216), which is based on Nipype 1.5.1 (Gorgolewski et al. (2011); Gorgolewski et al. (2018); RRID:SCR_002502).

Anatomical data preprocessing

A total of 1 T1-weighted (T1w) images were found within the input BIDS dataset.The T1-weighted (T1w) image was corrected for intensity non-uniformity (INU) with `N4BiasFieldCorrection` (Tustison et al. 2010), distributed with ANTs 2.3.3 (Avants et al. 2008, RRID:SCR_004757), and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped with a Nipype implementation of the `antsBrainExtraction.sh` workflow (from ANTs), using OASIS30ANTs as target template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using `fast` (FSL 5.0.9, RRID:SCR_002823, Zhang, Brady, and Smith 2001). Brain surfaces were reconstructed using `recon-all` (FreeSurfer 6.0.1, RRID:SCR_001847, Dale, Fischl, and Sereno 1999), and the brain mask estimated previously was refined with a custom variation of the method to reconcile ANTs-derived and FreeSurfer-derived segmentations of the cortical gray-matter of Mindboggle (RRID:SCR_002438, Klein et al. 2017). Volume-based spatial normalization to one standard space (MNI152NLin2009cAsym) was performed through nonlinear registration with `antsRegistration` (ANTs 2.3.3), using brain-extracted versions of both T1w reference and the T1w template. The following template was selected for spatial normalization: ICBM 152 Nonlinear Asymmetrical template version 2009c [Fonov et al. (2009), RRID:SCR_008796; TemplateFlow ID: MNI152NLin2009cAsym],

Functional data preprocessing

For each of the 1 BOLD runs found per subject (across all tasks and sessions), the following preprocessing was performed. First, a reference volume and its skull-stripped version were generated by aligning and averaging 1 single-band references (SBRefs). A B0-

nonuniformity map (or fieldmap) was estimated based on two (or more) echo-planar imaging (EPI) references with opposing phase-encoding directions, with `3dQwarp` Cox and Hyde (1997) (AFNI 20160207). Based on the estimated susceptibility distortion, a corrected EPI (echo-planar imaging) reference was calculated for a more accurate co-registration with the anatomical reference. The BOLD reference was then co-registered to the T1w reference using `bbregister` (FreeSurfer) which implements boundary-based registration (Greve and Fischl 2009). Co-registration was configured with six degrees of freedom. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) are estimated before any spatiotemporal filtering using `mcflirt` (FSL 5.0.9, Jenkinson et al. 2002). BOLD runs were slice-time corrected using `3dTshift` from AFNI 20160207 (Cox and Hyde 1997, RRID:SCR_005927). First, a reference volume and its skull-stripped version were generated using a custom methodology of fMRIPrep. The BOLD time-series (including slice-timing correction when applied) were resampled onto their original, native space by applying a single, composite transform to correct for head-motion and susceptibility distortions. These resampled BOLD time-series will be referred to as preprocessed BOLD in original space, or just preprocessed BOLD. The BOLD time-series were resampled into standard space, generating a preprocessed BOLD run in MNI152NLin2009cAsym space. First, a reference volume and its skull-stripped version were generated using a custom methodology of fMRIPrep. Several confounding time-series were calculated based on the preprocessed BOLD: framewise displacement (FD), DVARS and three region-wise global signals. FD was computed using two formulations following Power (absolute sum of relative motions, Power et al. (2014)) and Jenkinson (relative root mean square displacement between affines, Jenkinson et al. (2002)). FD and DVARS are calculated for each functional run, both using their implementations in Nipype (following the definitions by Power et al. 2014). The three global signals are extracted within the CSF, the WM, and the whole-brain masks. Additionally, a set of physiological regressors were extracted to allow for component-based noise correction (CompCor, Behzadi et al. 2007). Principal components are estimated after high-pass filtering the preprocessed BOLD time-series (using a discrete cosine filter with 128s cut-off) for the two CompCorvariants: temporal (tCompCor) and anatomical (aCompCor). tCompCor components are then calculated from the top 2% variable voxels within the brain mask. For aCompCor, three probabilistic masks (CSF, WM and combined CSF+WM) are

generated in anatomical space. The implementation differs from that of Behzadi et al. in that instead of eroding the masks by 2 pixels on BOLD space, the aCompCor masks are subtracted a mask of pixels that likely contain a volume fraction of GM. This mask is obtained by dilating a GM mask extracted from the FreeSurfer's aseg segmentation, and it ensures components are not extracted from voxels containing a minimal fraction of GM. Finally, these masks are resampled into BOLD space and binarized by thresholding at 0.99 (as in the original implementation). Components are also calculated separately within the WM and CSF masks. For each CompCor decomposition, the k components with the largest singular values are retained, such that the retained components' time series are sufficient to explain 50 percent of variance across the nuisance mask (CSF, WM, combined, or temporal). The remaining components are dropped from consideration. The head-motion estimates calculated in the correction step were also placed within the corresponding confounds file. The confound time series derived from head motion estimates and global signals were expanded with the inclusion of temporal derivatives and quadratic terms for each (Satterthwaite et al. 2013). Frames that exceeded a threshold of 0.5 mm FD or 1.5 standardised DVARS were annotated as motion outliers. All resamplings can be performed with a single interpolation step by composing all the pertinent transformations (i.e. head-motion transform matrices, susceptibility distortion correction when available, and co-registrations to anatomical and output spaces). Gridded (volumetric) resamplings were performed using `antsApplyTransforms` (ANTs), configured with Lanczos interpolation to minimize the smoothing effects of other kernels (Lanczos 1964). Non-gridded (surface) resamplings were performed using `mri_vol2surf` (FreeSurfer).

Many internal operations of fMRIPrep use Nilearn 0.6.2 (Abraham et al. 2014, RRID:SCR_001362), mostly within the functional processing workflow. For more details of the pipeline, see the section corresponding to workflows in fMRIPrep's documentation.

References for Appendix B

Abraham, Alexandre, Fabian Pedregosa, Michael Eickenberg, Philippe Gervais, Andreas Mueller, Jean Kossaifi, Alexandre Gramfort, Bertrand Thirion, and Gael Varoquaux. 2014. "Machine Learning for Neuroimaging with Scikit-Learn." Frontiers in Neuroinformatics 8. https://doi.org/10.3389/fninf.2014.00014.

Avants, B.B., C.L. Epstein, M. Grossman, and J.C. Gee. 2008. "Symmetric Diffeomorphic Image Registration with Cross-Correlation: Evaluating Automated Labeling of Elderly and Neurodegenerative Brain." Medical Image Analysis 12 (1): 26–41. https://doi.org/10.1016/j.media.2007.06.004.

Behzadi, Yashar, Khaled Restom, Joy Liau, and Thomas T. Liu. 2007. "A Component Based Noise Correction Method (CompCor) for BOLD and Perfusion Based fMRI." NeuroImage 37 (1): 90–101. https://doi.org/10.1016/j.neuroimage.2007.04.042.

Cox, Robert W., and James S. Hyde. 1997. "Software Tools for Analysis and Visualization of fMRI Data." NMR in Biomedicine 10 (4-5): 171–78. https://doi.org/10.1002/(SICI)1099-1492(199706/08)10:4/5<171::AID-NBM453>3.0.CO;2-L.

Dale, Anders M., Bruce Fischl, and Martin I. Sereno. 1999. "Cortical Surface-Based Analysis: I. Segmentation and Surface Reconstruction." NeuroImage 9 (2): 179–94. https://doi.org/10.1006/nimg.1998.0395.

Esteban, Oscar, Ross Blair, Christopher J. Markiewicz, Shoshana L. Berleant, Craig Moodie, Feilong Ma, Ayse Ilkay Isik, et al. 2018. "FMRIPrep." Software. Zenodo. https://doi.org/10.5281/zenodo.852659.

Esteban, Oscar, Christopher Markiewicz, Ross W Blair, Craig Moodie, Ayse Ilkay Isik, Asier Erramuzpe Aliaga, James Kent, et al. 2018. "fMRIPrep: A Robust Preprocessing Pipeline for Functional MRI." Nature Methods. https://doi.org/10.1038/s41592-018-0235-4.

Fonov, VS, AC Evans, RC McKinstry, CR Almli, and DL Collins. 2009. "Unbiased Nonlinear Average Age-Appropriate Brain Templates from Birth to Adulthood." NeuroImage 47, Supplement 1: S102. https://doi.org/10.1016/S1053-8119(09)70884-5.

Gorgolewski, K., C. D. Burns, C. Madison, D. Clark, Y. O. Halchenko, M. L. Waskom, and S. Ghosh. 2011. "Nipype: A Flexible, Lightweight and Extensible Neuroimaging Data Processing Framework in Python." Frontiers in Neuroinformatics 5: 13. https://doi.org/10.3389/fninf.2011.00013.

Gorgolewski, Krzysztof J., Oscar Esteban, Christopher J. Markiewicz, Erik Ziegler, David Gage Ellis, Michael Philipp Notter, Dorota Jarecka, et al. 2018. "Nipype." Software. Zenodo. https://doi.org/10.5281/zenodo.596855.

Greve, Douglas N, and Bruce Fischl. 2009. "Accurate and Robust Brain Image Alignment Using Boundary-Based Registration." NeuroImage 48 (1): 63–72. https://doi.org/10.1016/j.neuroimage.2009.06.060.

Jenkinson, Mark, Peter Bannister, Michael Brady, and Stephen Smith. 2002. "Improved Optimization for the Robust and Accurate Linear Registration and Motion Correction of Brain Images." NeuroImage 17 (2): 825–41. https://doi.org/10.1006/nimg.2002.1132.

Klein, Arno, Satrajit S. Ghosh, Forrest S. Bao, Joachim Giard, Yrjö Häme, Eliezer Stavsky, Noah Lee, et al. 2017. "Mindboggling Morphometry of Human Brains." PLOS Computational Biology 13 (2): e1005350. https://doi.org/10.1371/journal.pcbi.1005350.

Lanczos, C. 1964. "Evaluation of Noisy Data." Journal of the Society for Industrial and Applied Mathematics Series B Numerical Analysis 1 (1): 76–85. https://doi.org/10.1137/0701007.

Power, Jonathan D., Anish Mitra, Timothy O. Laumann, Abraham Z. Snyder, Bradley L. Schlaggar, and Steven E. Petersen. 2014. "Methods to Detect, Characterize, and Remove Motion Artifact in Resting State fMRI." NeuroImage 84 (Supplement C): 320–41. https://doi.org/10.1016/j.neuroimage.2013.08.048.

Satterthwaite, Theodore D., Mark A. Elliott, Raphael T. Gerraty, Kosha Ruparel, James Loughead, Monica E. Calkins, Simon B. Eickhoff, et al. 2013. “An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state functional connectivity data.” NeuroImage 64 (1): 240–56. https://doi.org/10.1016/j.neuroimage.2012.08.052.

Tustison, N. J., B. B. Avants, P. A. Cook, Y. Zheng, A. Egan, P. A. Yushkevich, and J. C. Gee. 2010. “N4ITK: Improved N3 Bias Correction.” IEEE Transactions on Medical Imaging 29 (6): 1310–20. https://doi.org/10.1109/TMI.2010.2046908.

Zhang, Y., M. Brady, and S. Smith. 2001. “Segmentation of Brain MR Images Through a Hidden Markov Random Field Model and the Expectation-Maximization Algorithm.” IEEE Transactions on Medical Imaging 20 (1): 45–57. https://doi.org/10.1109/42.906424.