Deconstructing Depression:

A Symptom-Level Investigation of Genetic Risk, Brain Morphology, and Treatment Effects

by

Giulia Piazza

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Doctor in Philosophy

in

Psychiatric Epidemiology and Genetics

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Faculty of Brain Sciences

University College London

Declaration

I, Giulia Piazza, confirm that the work presented in my thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Giulia Piazza

Abstract

Background: Depression can consist of many combinations of heterogeneous symptoms, which are often shared with other disorders. Despite this complexity, symptoms are typically aggregated into summary scores, potentially obscuring key insights into the origins and treatment of depression. To remedy this, my thesis deconstructs depression by adopting a symptom-level approach, allowing me to provide novel insights into the genetic origins, underlying neurobiological mechanisms, and sensitivity to treatment of depression and its comorbidities.

Methods: In the first study, I examine the link between genetic risk and individual indicators of childhood psychopathology, combining network analysis and polygenic scores for depression and related traits. This study uses data from the Avon Longitudinal Study of Parents and Children (ALSPAC) and replicates findings in the Twins Early Development Study (TEDS). The second study builds on these findings by exploring the associations between genetic risk, regional brain volumes, and symptoms of depression and anxiety in a sample of adults from the UK Biobank. Using a mediation approach, I assess whether regional brain volumes mediate the relationship between polygenic scores for mental health disorders and individual symptoms. The third study evaluates the effects of the selective serotonin reuptake inhibitor sertraline on individual symptoms of depression and anxiety and their longitudinal associations, using data from the PANDA ("What are the indications for Prescribing ANtiDepressAnts that will lead to a clinical benefit?") randomised controlled trial.

Results: This thesis yields three key findings. First, polygenic scores for traits relevant to depression are associated with a restricted set of cross-trait and trait-relevant symptoms, suggesting that specific components of depression and comorbid disorders may drive associations between genetic risk and psychiatric phenotypes. Second, regional brain volumes are associated with a subset of symptoms of depression and anxiety, indicating that symptoms may differ in the extent to which they are linked to brain morphology. Third, sertraline affects core emotional and volitional symptoms, with beneficial effects emerging after two weeks of treatment, earlier than previously reported. Beneficial effects may be hidden by concurrent detrimental effects on somatic indicators when aggregating symptoms into summary scores.

Conclusions: These findings highlight the potential of symptom-level approaches to uncover patterns of associations that advance our understanding of depression and its comorbidities. Aggregating heterogeneous symptoms of depression can hide granular information on the genetic aetiology, brain mechanisms and treatment response in psychopathology.

Impact Statement

Implications and contributions

The findings presented in this thesis provide novel insights into the symptomatology of depression and related disorders by uncovering links between specific symptoms and genetic risk, brain structure, and response to antidepressant treatment. These findings may have important implications for both research and clinical practice, as well as broader contributions to open science and science communication.

Research implications

This thesis reveals previously unreported associations between genetic and neurobiological factors and specific symptoms of depression and anxiety. By adopting a symptom-level approach, the findings demonstrate that studying individual symptoms, rather than relying on diagnostic categories, yields more precise and informative insights into mental health disorders. Additionally, moving beyond the aggregation of heterogeneous symptoms, this work challenges traditional classification systems and supports the development of novel, aetiologically-informed frameworks to capture the complexity of psychopathology.

Clinical implications

The findings indicate that selective serotonin reuptake inhibitors can have both beneficial and detrimental effects on symptoms of depression and anxiety, with physical and psychological effects detected earlier than previously recognised. These insights contribute to refining treatment selection and

personalisation, informing clinicians and patients of the complex effects of antidepressants. Moreover, this thesis supports the use of approaches based on formulation in therapy practice, which take into consideration a patient's symptoms and their interconnections.

Open science practices

I shared all code relevant to produce results from this thesis on Github and pre-registered the replication of findings in Chapter 2.

Dissemination

I actively sought to disseminate my research and presented the findings from my thesis at national and international conferences, including:

- World Congress of Psychiatric Genetics (Florence, September 2022)
- Behavioural Genetics Association annual meeting (Murcia, June 2023)
- British Psychopharmacology Association summer meeting (Manchester, July 2023, and Birmingham, July 2024)
- UCL Early Career Researchers in Children and Young People Conference (London, 2023)
- UCL Institute of Mental Health Conference (London, August 2022 and August 2023)

Additionally, I am committed to communicating science to wider audiences and have written blogs for Psychology Today and the Mental Elf.

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Chapter 1: General Introduction

1.1 Contextual background

Mental health disorders are defined and measured in various ways, but most approaches rely on assessing individual symptoms, which contribute to establishing a diagnosis. People living with mental health disorders differ substantially in the number and combination of symptoms they experience, leading to considerable variability in symptom profiles underlying a single diagnosis. Moreover, symptoms are heterogeneous, differing in origin, clinical manifestation, and impact on functioning. Despite this complexity, most research studies measure mental health conditions on a continuum, typically using aggregate scores. Aggregate scores, however, do not adequately account for symptom heterogeneity or fully capture the distinct features of a disorder. This issue is especially evident in the case of depression, which is characterised by a complex, multifactorial structure and diverse clinical presentations. Measuring depression with summary scores can limit research on its causes, underlying mechanisms, and treatments.

Therefore, this thesis focuses on demonstrating how a symptom-level approach to phenotyping can reveal new insights into the aetiology, pathology and treatment of depression and anxiety. To that end, I use a combination of network analysis and genetic epidemiology methods, applied to large population-based cohorts and clinical data. In this introduction, I first review the literature on symptom heterogeneity in depression (Section 1.2) and its impact on our understanding of comorbidity, brain correlates, and clinical interventions. Next, I examine symptom-level approaches to psychopathology

(Section 1.3), emphasising network theory, network analysis, and structural equation modelling. Finally, I outline the remaining chapters of this thesis (Section 1.4). High resolution plots and figures in the thesis are available online.

1.2 Symptom heterogeneity in depression

1.2.1 A symptom-based definition of depression

Major Depressive Disorder (MDD), or depression, is a common mental health condition characterised by changes in emotions, behaviour, and cognition (Otte et al., 2016). Depression has been defined across a variety of reference and classification manuals of mental health disorders, particularly over the last two centuries. Among these manuals, the Diagnostic and Statistical Manual of Mental Disorders (DSM, American Psychiatric Association, 2013) details standard criteria for diagnosing mental health disorders and serves as a widely used guide for mental health practitioners and researchers. First published by the American Psychiatric Association in 1952 and now in its fifth edition, the DSM stipulates that a diagnosis of depression requires the presence of at least five out of nine listed symptoms during a two-week period, with one symptom being either persistent low mood or anhedonia (a lack of interest or enjoyment of activities) (American Psychiatric Association, 2013). Other symptoms include fatigue, problems with appetite, sleep, libido and concentration, psychomotor issues, feelings of guilt and worthlessness, thoughts of death, and suicidal ideation (Otte et al., 2016). Depression can be highly debilitating, often leading to substantial functional impairment. In fact, it is a leading contributor to the global disease burden, accounting for the largest proportion

of Disability Adjusted Life Years (DALYs) attributed to mental disorders (GBD 2019 Mental Disorders Collaborators, 2022; Mathers & Loncar, 2006; World Health Organisation, 2023).

The ambiguity of a symptom-based definition can lead to substantial variability in the clinical presentation of depression. Hundreds of unique combinations of symptoms satisfy the criteria for a depression diagnosis (Buch & Liston, 2021; Fried & Nesse, 2015), with some symptoms manifesting in opposite ways (e.g., hypersomnia vs. insomnia, weight gain vs. weight loss, psychomotor agitation vs. retardation). For instance, an analysis of a large sample of depressed patients (N=3,703) revealed over 1,000 distinct symptom combinations (Fried & Nesse, 2015). Similarly, the DSM-5 melancholic specifier, intended to identify a homogenous depression subgroup, can be satisfied by more than 10,000 distinct presentations (Fried et al., 2020). This considerable symptom variability has been observed both across individuals and within individuals over time (Oquendo et al., 2004), and it can affect how we think of comorbidity in mental health disorders.

1.2.2 Comorbidity and symptom overlap

Depression almost always co-occurs with other mental and physical disorders, such as anxiety disorders and substance use. Most individuals with psychiatric disorders experience two or more lifetime diagnoses (Barr et al., 2022; Kessler et al., 2005) and may develop multiple disorders consecutively (Caspi et al., 2020). Those who meet the criteria for more than one disorder tend to have a worse prognosis (Nock et al., 2010) and a more severe course of illness (Angst et al., 2002). However, the high prevalence of comorbidity suggests that it may

be, in part, an artefact of current classification systems. In fact, there is considerable symptom overlap across mental health disorders (Forbes et al., 2023). For instance, depression and generalised anxiety disorder (GAD) both feature fatigue, concentration problems, and disrupted sleep. This symptom overlap can inflate estimates of the covariation between disorders (Forbes, 2023) and introduce a potential source of systematic error in research (i.e., bias).

Moreover, depression symptoms are far from unique to the disorder. A recent descriptive study mapped the repetition of individual symptoms across DSM-5 diagnoses, finding that depression symptoms ranked in the top 10 most repeated (Forbes et al., 2023). Specifically, insomnia, hypersomnia, and poor concentration were the most common symptoms, each occurring in over 16 diagnoses. In contrast, the majority of symptoms of other mental health disorders were found to be specific to a single diagnosis (Forbes et al., 2023). Therefore, the poor specificity of depressive symptoms suggests that they are overly general indicators of the disorder. An excessively broad, symptom-based definition poses a challenge to research into the causes and consequences of depression.

1.2.3 Aetiology and impact of depression symptoms

Studies have shown that depression is associated with several environmental and genetic risk factors (Bromet et al., 2011; Kendall et al., 2021; Otte et al., 2016). Demographic characteristics (such as female gender or low socioeconomic status) and stressful life events (such as adverse childhood experiences or loss of a spouse) increase the risk for depression and lead to

worse outcomes (Kessler & Bromet, 2013; Lorant, 2003; Seedat et al., 2009). Additionally, depression is a moderately heritable disorder (Kendall et al., 2021; Polderman et al., 2015) (Section 1.2.4) with a complex pathobiology that substantially involves the brain (Hamilton et al., 2012; Kempton et al., 2011; Schmaal et al., 2020) (Section 1.2.5). Despite the development of effective psychological and pharmacological interventions, treatment outcomes are highly variable, with around half of patients not responding to antidepressant medication, and modest effect sizes on average (Cipriani et al., 2018; Cuijpers et al., 2023; Trivedi et al., 2006; Warden et al., 2007) (Section 2.6).

Notably, individual depression symptoms appear to be differentially impacted by various risk factors, such as sex and depression history (Fried et al., 2014). For example, evidence suggests that symptoms are associated with different adverse life events (Keller et al., 2007; Keller & Nesse, 2005, 2006), with social losses (such as isolation and grief) primarily linked to crying and sadness, and chronic stress more closely associated with fatigue and hypersomnia (Keller et al., 2007). Additionally, depression symptoms were found to vary in their association with psychosocial impairment (Fried & Nesse, 2014). Specifically, sad mood, concentration problems, fatigue and anhedonia explained the largest proportion of variance in impairment, while weight problems and insomnia contributed the least (Fried & Nesse, 2014). Therefore, symptoms of depression do not appear to be equally important, as they may be affected differently by risk factors and may, in turn, contribute differently to health outcomes.

Taken together, these findings suggest that depression symptoms are not interchangeable indicators of the disorder, but instead reflect distinct, heterogeneous properties. Such symptom heterogeneity complicates efforts to understand the nature of comorbidity and the influence of risk factors on depression, such as the influence of genetics.

1.2.4 The genetic structure of depression symptoms

Depression tends to cluster within families, with a heritability estimate (h^2) of approximately 34-45%, indicating that around 34-45% of the variability in depression is attributable to genetic factors (Polderman et al., 2015). Genetic studies have shown that depression is a complex polygenic disorder, influenced by many genetic variants across the genome, each exerting a small effect.

In fact, a recent genome-wide association study (GWAS) identified 697 independent genetic variants linked to depression in a sample of over 5 million individuals (McIntosh et al., 2024). These variants accounted for around 8.4% of the variance in depression (the proportion of variance explained by common single nucleotide polymorphisms, or SNP-based heritability, h_{SNP}) (**Figure 1.1**) in European ancestries. This figure falls short of the narrow sense heritability of twin studies (i.e., h^2=34-45%), and larger sample sizes may be needed to fully recover this “missing heritability” (i.e., the difference between traditional heritability estimates, and heritability estimates derived from molecular genetics studies, such as GWASs) (Maher, 2008; Matthews & Turkheimer, 2022).

The way depression is measured, however, impacts findings from GWASs, with narrower, diagnosis-based phenotypes generally yielding higher estimates of heritability than broader phenotypes based on self-reported symptoms. For example, a recent GWAS found lower SNP-heritability when defining depression cases via self-reported symptoms ('minimal' phenotyping; h_{SNP}=11%) compared to using full diagnostic criteria for MDD (h_{SNP}=26%) (N. Cai et al., 2019), a result which was not explained by the inclusion of milder cases in the 'minimal' phenotype group. Notably, SNP-based heritability estimates of individual symptoms range from 6% for concentration problems to 9% for appetite changes (Thorp et al., 2020). Although these symptom-specific estimates were obtained from a moderately sized sample for genetic analyses (~150,000 individuals) and need replication, they suggest that genetic factors may have a stronger influence on some features of depression.

The effect size estimates obtained from GWASs can be aggregated to derive polygenic scores (PGSs; **Figure 1.1**). PGSs are weighted sums of risk alleles carried by an individual, which index their propensity for a particular trait (Evans et al., 2009; International Schizophrenia Consortium et al., 2009). PGS studies have revealed considerable overlap across psychiatric traits, indicating that the genetic structure of mental health disorders does not align with distinct diagnostic categories. For example, the PGS for depression predicts not only depression itself (Howard et al., 2019) but also other conditions, such as bipolar disorder, anxiety disorders (Shi et al., 2022) and substance use (Andersen et al., 2017; Gurriarán et al., 2019; Shi et al., 2022).

These cross-trait PGS associations could reflect common underlying mechanisms across comorbid disorders. For instance, the same genetic variants could influence co-occurring disorders (i.e., pleiotropy). Indeed, co-occurring mental and physical disorders are genetically correlated (Meijsen et al., 2024), which suggests that shared genetic factors may contribute to comorbidity. However, genetic correlations may also be inflated by symptom overlap. For example, the shared genetic liability between anxiety and depression could partially result from genetic influences on common symptoms, such as fatigue, insomnia, and concentration problems.

However, few genetic studies have focused on individual symptoms (e.g., Isvoranu et al., 2020). Most research has relied on aggregate depression scores, and no studies have investigated the polygenic risk for depression at the level of individual symptoms. This gap is addressed in Chapter 2, where I adopt a symptom-level approach to examine associations between PGSs for traits relevant to psychiatric disorders (depression, anxiety, attention deficit-hyperactivity disorder [ADHD], educational attainment and body mass index [BMI]) and individual psychopathology symptoms (Chapter 2).

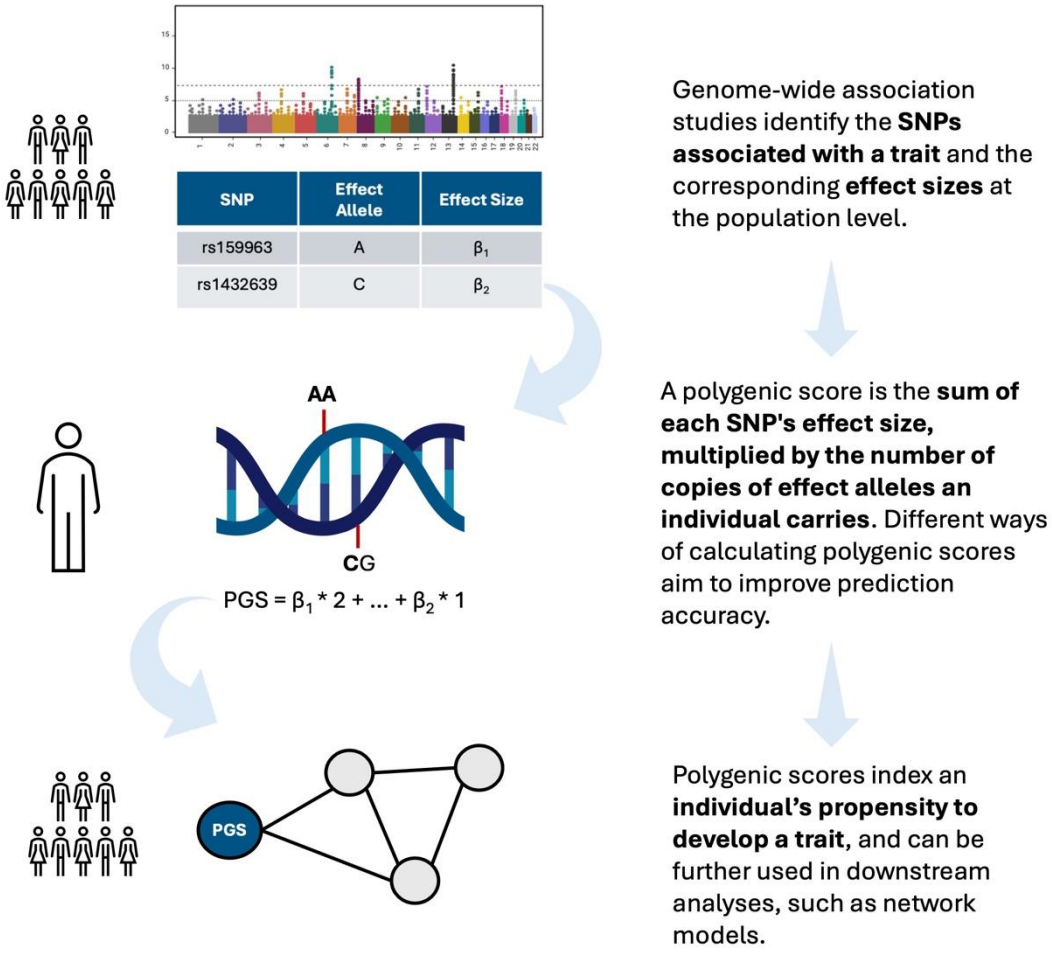


Figure 1.1: Deriving polygenic scores from genome-wide association studies' summary statistics for downstream analyses (e.g., psychological networks).
SNP = single nucleotide polymorphism; PGS = polygenic score.

1.2.5 Transdiagnostic brain features

Genetic studies suggest that variants associated with an increased risk of depression may be expressed in the brain, with links to specific cell types (e.g., neurons) (McIntosh et al., 2024; Wray et al., 2018) and neurotransmission pathways (Howard et al., 2019). Brain structure and function may be closely related to genetic activity and, therefore, can be considered intermediate phenotypes between genes and behaviour (Buch & Liston, 2021). These brain markers are heritable, polygenic, and genetically correlated with mental health disorders (Buch & Liston, 2021; M. Liu et al., 2024; S. Liu, Smit, et al., 2023). Patterns of alterations in brain structure have been shown to distinguish depressed patients from healthy controls (Schmaal et al., 2020), and such alterations can also be observed in unaffected family members (Chai et al., 2015). Consequently, brain measures may offer insights into the mechanisms underlying mental health disorders by going beyond genotype-phenotype associations.

Specifically, neuroimaging studies have shown depression is associated with lower cortical and subcortical volumes in several brain regions, including the hippocampus, orbitofrontal cortex, cingulate, and temporal lobes (Schmaal et al., 2016, 2017). Genetic influences on depression may therefore be partially mediated by influences on brain structure. However, neuroimaging studies, much like genetic studies, require large sample sizes and rigorous statistical correction for multiple comparisons (S. Liu, Abdellaoui, et al., 2023). Early studies, which were typically underpowered, often failed to replicate and likely led to overestimates of the association between depression and brain structure and function. Recent collaborations, such as Enhancing Neuro

Imaging Genetics through Meta-Analysis (ENIGMA) (Thompson et al., 2021), have addressed these issues by focusing on large sample sizes, meta-analytic approaches and coordinated analytical pipelines.

Large-scale studies have revealed considerable overlap across mental health disorders in brain regions exhibiting altered structure and function (McCutcheon et al., 2023). In fact, there is more evidence for commonalities in neural dysfunction than for distinct brain alterations across disorders (Goodkind et al., 2015; Vanes & Dolan, 2021). While these shared attributes may reflect shared mechanistic processes, symptom overlap may also lead to an overestimation of these similarities. Notably, research has linked individual depression symptoms to the volumes of specific brain areas (Freichel et al., 2024; Hilland et al., 2020). For example, hippocampus volume is primarily associated with symptoms such as anhedonia, sadness, irritability, and appetite problems (Freichel et al., 2024). These findings further highlight the complexity of the biological underpinnings of depression, suggesting that its genetic and neural bases do not neatly align with diagnostic categories.

Despite the challenges posed by symptom overlap and symptom heterogeneity, neuroimaging genetics studies typically rely on aggregate scores to measure depression. This approach overlooks symptom-level associations that could provide a more nuanced understanding of the relationships between genetic risk, brain structure, and mental health. Notably, no study has yet employed a symptom-level approach to link these levels of explanation. In Chapter 3, I address this gap by investigating the associations between the genetic risk for psychiatric disorders, volumetric brain measures,

and individual symptoms. Chapter 3 focuses on depression and co-occurring disorders, such as ADHD, schizophrenia, and bipolar disorder, which share both patterns of structural abnormalities and genetic influences with depression. Specifically, I examine whether brain structure – including the volume of the hippocampus, insula, cingulate, fusiform and medial orbitofrontal cortex - mediates the association between PGSs and symptoms of depression and anxiety.

In summary, the findings presented so far in this section highlight the downsides of using aggregate scores to measure depression, which may lead to neglecting important heterogeneity in symptoms, and thus impact our understanding of the genetic risk for depression and its brain correlates. To add to this evidence, I now turn to discussing the impact of symptom heterogeneity and symptom overlap on the treatment of depression.

1.2.6 Variability in treatment outcomes

The comorbidity between depression and other disorders complicates the treatment of these conditions. While psychotherapy and pharmacotherapy are effective first-line interventions for depression, treatment outcomes vary significantly and have at best moderate effect sizes when aggregated across patients. Recovery rates range from 40% to 70% (Dalgleish et al., 2020), with poorer outcomes observed in individuals with multiple comorbid conditions (Hung et al., 2020; Ter Meulen et al., 2021). Despite the prevalence of comorbidity, transdiagnostic interventions—designed to address multiple co-occurring conditions—remain uncommon (Dalgleish et al., 2020; Moses & Barlow, 2006). Instead, treatment approaches are often informed by

diagnoses, potentially exacerbating variability in outcomes by overlooking the impact of diagnostic overlap and symptom heterogeneity.

In particular, selective serotonin reuptake inhibitors (SSRIs) are among the first-line treatments for both depression and anxiety, but their efficacy is moderate (Cipriani et al., 2018). Approximately half of patients respond to SSRIs, and only about one-third achieve remission with an initial SSRI in the first 3 to 4 months of treatment (Trivedi et al., 2006; Warden et al., 2007). SSRIs primarily target serotonin and noradrenaline neurotransmitter systems (Rang et al., 2012), yet clinically significant improvements in mood typically require 4–6 weeks of treatment (Walsh & Harmer, 2015). This delay may reflect the time required for downstream neuroadaptive processes to take effect. However, this timing could also stem from the limitations of current diagnostic frameworks, which rely on symptom-based definitions.

Notably, individual symptoms of depression and anxiety respond differently to treatment. For example, SSRIs were found to be particularly effective in addressing core emotional symptoms, such as low mood and anxiety (Boschloo et al., 2019; Cervin et al., 2020; Komulainen et al., 2021; Zhou et al., 2022). A secondary analysis of data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial revealed differential treatment effects across three clusters of depression symptoms, with a replication of these findings in an independent sample (Chekroud et al., 2017). Core emotional symptoms (such as depressed mood and anhedonia) improved more than atypical symptoms like psychomotor issues and libido changes, with trajectories differing across SSRI types. Similarly, a

comprehensive analysis of 18 clinical trials compared the efficacy of common SSRIs against placebo using the Hamilton Depression Rating Scale (HDRS-17) (Hieronymus et al., 2016). The results showed that SSRIs had a larger effect size on the single item 'depressed mood' compared to total HDRS-17 scores, highlighting that using aggregate scores may obscure important treatment effects of antidepressants (Hieronymus et al., 2016).

Despite these findings, studies on the effects of antidepressants on individual symptoms rarely incorporate placebo comparisons. Moreover, findings often do not account for the timing of symptom-specific responses, neglecting how antidepressant effects unfold over time. To address these issues, in Chapter 4, I analyse the effects of SSRIs on individual symptoms of depression and anxiety using data from a large Randomised Controlled Trial (RCT). Combining analyses at a single time point and across time, I investigate the effects of sertraline on individual symptoms and their reciprocal associations, compared to placebo.

1.2.7 Section summary

Depression is a complex, heritable disorder linked to dysfunction in several brain regions. Symptom heterogeneity poses a considerable challenge to depression research. Particularly, the findings presented in Section 1.2 suggest that individual symptoms of depression have substantially different characteristics and may not be exchangeable indicators of the underlying disorder. Aggregating symptoms in depression research may hide relevant information by neglecting this symptom heterogeneity. Adopting a dimensional, symptom-focused approach may further our understanding of

the genetic basis (Chapter 2), neural mechanisms (Chapter 3) and treatments (Chapter 4) for depression. In the following section (Section 1.3), I outline the symptom-level approaches adopted in this thesis.

1.3 Symptom-level approaches

1.3.1 The latent disorder approach to psychopathology

A prevailing, albeit usually unarticulated, assumption of psychopathology research – for example, case-control studies – is that symptoms are caused by latent mental health disorders that are not directly measurable (Bekhuis et al., 2019; Borsboom, 2017; Zachar, 2000). This perspective mirrors so-called "medical models"[1], positing that removing the common cause will eliminate the presenting symptoms (Kendler et al., 2011; van Praag, 2000). In this framework, symptoms are linked because they are caused by the same disorder, but are otherwise independent. Similarly, co-occurring symptoms are explained as arising from comorbid latent disorders (Cramer et al., 2010). For instance, under the common cause model, depression is conceptualised as a single disorder that causes symptoms, such as low mood and fatigue. Treating depression is thought to resolve these symptoms. In this framework, depression and anxiety are conceptualised as latent disorders that naturally co-occur, leading to correlations between their respective symptoms (Bringmann & Eronen, 2018).

[1] Note that although the "medical model" is often discussed in psychiatric literature, this term does not completely describe the range of problems dealt with in general medicine (e.g., disorders, syndromes, injuries, pathologies). For example, see Aftab, (2025).

The common cause theory is often tested using statistical models that aim to explain relationships between variables, such as latent factor models, where correlations between indicators are explained by latent common factors. In psychopathology (and other fields), however, variables are frequently positively correlated – a concept known as the 'positive manifold' (Eaton et al., 2023; van Bork et al., 2017). Alternative explanations to latent factors can equally account for this covariance structure, leading to a 'statistical equivalence' problem (Aristodemou & Fried, 2020). For instance, the general psychopathology factor 'p' has been proposed as an underlying dimension capturing the propensity to develop any psychiatric disorder (Caspi et al., 2014; Sprooten et al., 2022). Similarly, the bifactor model incorporates both a general factor, representing shared aspects of psychopathology, and specific factors, accounting for disorder-specific features (Koch et al., 2018).

Although p-factor and bifactor models can summarise data effectively, different data-generating mechanisms may give rise to identical correlation patterns among variables (Aristodemou et al., 2024; Aristodemou & Fried, 2020). Despite differences in complexity, these models are statistically nearly-equivalent and differ only in their theoretical implications (van Bork et al., 2017). Attempting to distinguish between these theoretical models using only statistical evidence, such as by comparing model fit, leads to inference errors (Aristodemou & Fried, 2020). In other words, interpreting the good fit of a latent factor model as evidence for the common cause theory would conflate theoretical and statistical models.

1.3.2 The network theory of psychopathology

Although the common cause theory of psychopathology has led to potentially important insights into mental health disorders, the parallel between psychological and physical disorders can fall somewhat short. For example, the human immunodeficiency virus (HIV) causes several symptoms, including fever and body rashes (Bringmann & Eronen, 2018). Fever, however, does not directly cause HIV rashes (i.e., there is no causal relationship between symptoms). HIV can also be asymptomatic, suggesting that it is a distinct entity from its symptoms. However, the same principles do not seem to hold for depression symptoms. For example, low self-esteem can cause concentration difficulties, leading to insomnia, which in turn can reinforce feelings of low self-esteem. Similarly, it is unclear whether depression can truly be asymptomatic.

Therefore, in contrast to latent factor approaches, network theory conceptualises mental disorders as constellations of co-occurring symptoms (Borsboom, 2017; Cramer et al., 2016). In this framework, symptoms are not assumed to be causally homogenous - that is, symptoms are not posited as the effects of a latent common cause. Instead, psychopathology is viewed as a complex dynamical system, in which mutual causal relationships between symptoms create maladaptive, self-reinforcing cycles (Borsboom, 2017; Cramer et al., 2010). Depression is thus considered the result of direct relationships between symptoms. Indeed, symptoms are not merely indicators of latent depression, but integral components of the disorder, which form predictable, interconnected patterns. In other words, depression is not conceptually distinct from its symptoms and cannot be asymptomatic.

Unlike the common cause model of psychopathology, network theory does not explain comorbidity as a direct relationship between latent disorders. Instead, it represents comorbid disorders as distinct symptom clusters connected by individual ‘bridge’ symptoms (Borsboom, 2017; Cramer et al., 2010). For example, anxiety and depression symptoms may form separate clusters, linked by overlapping symptoms, such as concentration problems, sleep disturbances, and fatigue. Comorbidity is thus conceptualised as the norm - an intrinsic characteristic of symptom networks, where symptom overlap is a natural feature, rather than an anomaly.

Network theory adopts a systemic approach to psychopathology, examining its individual components, their functions, and their interactions across levels of biological, psychological and social levels of analysis. External factors, such as risk factors, can give rise to specific symptoms in a network, thus ‘activating’ them (Borsboom, 2017; Fried et al., 2015). This activation can in turn spread to other, connected symptoms. For example, a stressful work environment can activate symptoms such as crying and sadness, which, in turn, may give rise to concentration and sleep problems. Furthermore, when symptoms have a strong tendency to activate each other, after a network has been strongly activated, simply removing the external factor (e.g., leaving a stressful job) may fail to deactivate it - a phenomenon known as ‘hysteresis’. Strongly connected symptom networks, where activation propagates easily, may indicate an individual’s high vulnerability to psychopathology and low resilience to stressful events (Borsboom, 2017).

It is important to note that network theory is in its early stages of development. While it has stimulated a growing body of innovative research, network theory is best understood as an organising framework, rather than a fully developed theory (Fried, 2020). For instance, the central claim that symptoms directly cause one another is difficult to falsify and may be excessively vague. That is, finding symptoms that do not cause each other would not necessarily disprove the theory, and finding a few symptoms that do cause each other would not provide conclusive confirmatory evidence. Advancing network theory will require more precise definitions (e.g., a clear definition of 'symptom') and formal descriptions of the expected causal relationships between specific symptoms (Fried, 2020), ideally in the form of clear, testable predictions. For example, Robinaugh et al. (2019) combined network theory, cognitive-behavioural theories, and computational modelling, formalising relationships between symptoms in panic disorder as sets of differential equations (Robinaugh et al., 2019) - an approach yet to be applied to depression.

Additionally, there is no clear dichotomy between common cause and network theories. Indeed, it is possible to conceive of intermediate options. For example, a latent disorder may cause individual symptoms and explain only part of their covariance, while the rest may be explained by direct causal relationships between symptoms (Bringmann & Eronen, 2018). Latent factors may also be interpreted non-causally, instead taken to represent characteristics common to psychopathology symptoms. The boundaries between these theoretical approaches are somewhat 'blurred'.

Therefore, in this thesis, I take a symptom-level approach to psychopathology, aiming to focus on the individual components of depression, rather than evaluating the validity of network theory, or formally comparing network and latent factor models. To analyse individual symptoms, I use a combination of network analysis (Section 1.3.3) and structural equation modelling (Section 1.3.5).

1.3.3 Network analysis

Network analysis is a statistical approach to the analysis of multivariate data, which can serve as a tool for generating hypotheses within network theory (Borsboom et al., 2021; Epskamp & Fried, 2018). Networks are graphical models that encode the joint probability distribution of a set of variables by focusing on pairwise relationships (Borsboom et al., 2021; Epskamp, Borsboom, et al., 2018; Epskamp & Fried, 2018). In psychological networks, individual symptoms are represented as nodes, while statistical associations between them are represented as edges (**Figure 1.2**). For example, nodes can correspond to individual items on a depression scale, and edges can represent partial correlations between these items (**Figure 1.2**).

Network analysis provides useful methods for estimating and visualising associations between symptoms in cross-sectional, longitudinal, and time-series data (Epskamp, Borsboom, et al., 2018; Epskamp, 2020). The first step in network estimation is typically node selection, which involves making decisions about which variables to include in a network (Borsboom et al., 2021). However, symptoms are often highly positively correlated, as scales are designed to maximise desirable psychometric qualities. This can lead to

issues of multicollinearity in network analysis. To address this, the number of nodes can be reduced based on a priori knowledge (e.g., combining variables that measure the same construct) or data-driven strategies (e.g., combining highly correlated variables), which help mitigate multicollinearity and improve network estimation (Borsboom et al., 2021; P. Jones, 2018).

Node selection is followed by edge selection, the process of statistically estimating conditional associations between variables (Borsboom et al., 2021). Common estimation approaches include model selection based on fit indices, null hypothesis testing, and cross-validation. The accuracy and robustness of edges can be assessed through network stability analyses (e.g., bootstrapping), and networks can be further described by examining their topological characteristics, such as node centrality, a measure of the relative importance of each node in a network (Epskamp & Fried, 2018).

Several limitations of network analysis should be considered. First, constructing robust and replicable networks requires large sample sizes relative to the number of estimated parameters, as well as careful selection of appropriate network estimators (Borsboom et al., 2021). Second, using single-item variables can introduce measurement imprecision, reducing reliability. Third, network results depend on the choice of nodes, as they represent conditional associations between variables (Epskamp, Waldorp, et al., 2018). Consequently, networks that include different nodes are not strictly comparable. Finally, associations between nodes may be confounded by unobserved common causes, making direct causal inferences based on networks rarely justifiable (Borsboom et al., 2021).

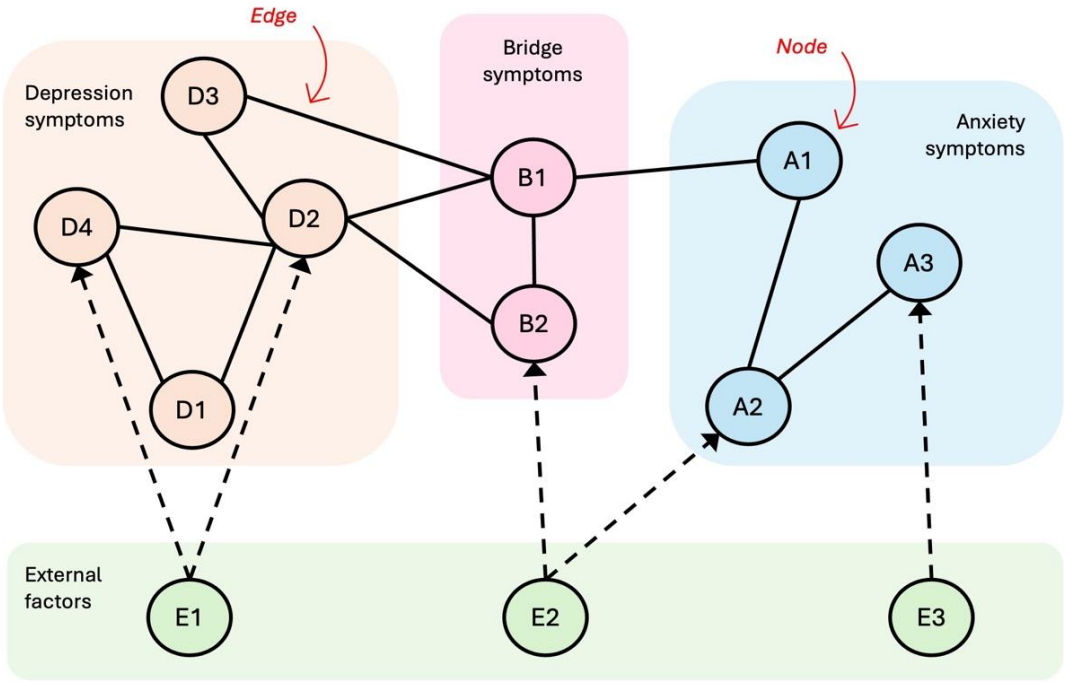


Figure 1.2: Schematic representation of networks of depression and anxiety symptoms. These networks can be connected by bridge symptoms (e.g., shared symptoms such as concentration problems and fatigue), and influenced by external factors (e.g., risk factors).

1.3.4 Relevant insights from network studies

The number of studies employing network analysis has grown exponentially in the last decade, leading to novel insights into the structure of symptoms of psychopathology. Early network research showed that symptoms tend to form diagnosis-like clusters, linked by shared symptoms (Cramer et al., 2010). For example, DSM-defined symptoms cluster around typical DSM diagnoses, though these clusters are not entirely distinct (Fried et al., 2016). Furthermore, research indicates that depression and anxiety symptoms are highly interconnected both in adulthood and across development, suggesting that comorbidity between depression and anxiety may be partially driven by symptom-level associations (Boschloo et al., 2015, 2016; McElroy et al., 2018; Rouquette et al., 2018).

Moreover, by modelling both external influences and symptoms of psychopathology, network studies can identify which symptoms are associated with specific risk factors. For example, one network study combined network analysis with polygenic scoring, showing that the PGS for schizophrenia is associated primarily with positive symptoms of the disorder (Isvoranu et al., 2020). Similarly, PGSs for systemic inflammatory markers are associated exclusively with somatic symptoms of depression (Kappelmann et al., 2021). However, no study (prior to the work carried out in this PhD) incorporated PGSs for depression (and other relevant psychiatric traits) in networks of psychopathology symptoms. Chapter 2 addresses this gap by investigating the associations between PGSs for depression, ADHD, anxiety,

BMI and educational attainment with symptoms of behavioural and emotional difficulties in childhood.

Additionally, few network studies have integrated genetic data and brain phenotypes into symptom networks. For instance, one study combined neuroimaging and behavioural data to examine the link between depression symptoms and brain structure, finding that regional volumes are not uniformly associated with all symptoms (Freichel et al., 2024). In Chapter 3, I expand on this approach by combining genetic, neuroimaging and symptom-level data. Specifically, I consider the mediating role of regional brain volumes in the association between PGSs for mental health disorders and symptoms of depression and anxiety.

Lastly, network studies have suggested that antidepressant treatment is associated with improvements in specific symptoms of depression and anxiety, such as guilt, low mood, and worry. For example, secondary analyses of the STAR*D trial identified loss of energy, low mood and anxious feelings as the most central (i.e., important) symptoms (Fried & Nesse, 2015; Madhoo & Levine, 2016). Similarly, a recent study reported that SSRI treatment led to improvements in guilt, suicidal thoughts, somatic symptoms and anxious feelings (Boschloo et al., 2019). However, most network studies have relied on cross-sectional comparisons of networks before and after treatment, rarely including placebo groups. Critically, no studies have directly compared the effects of SSRIs and placebo on symptoms at a single time point and across time. Chapter 4 addresses this gap by examining the effects of the SSRI

sertraline on individual symptoms of depression and anxiety both in comparison to placebo and over time.

1.3.5 A brief comparison of factor and network models

Although network analysis provides key tools designed to focus on individual symptoms of psychopathology, other approaches can be adapted to the study of symptoms. Structural equation modelling (SEM), for example, is typically used to model latent factors, but can also be adapted to model observed variables, such as aggregate scores or individual scale items (Bollen, 1989; Kline, 2011). While network models derive from graph theory, SEM stems from path analysis and has a longer history of methodological development for psychological variables, often providing more flexible analytical options than network analysis. Conversely, network analysis uniquely represents associations between variables, employing algorithms, such as the Fruchterman-Reingold algorithm, to easily and systematically visualise these relationships (Borsboom et al., 2021; Fruchterman & Reingold, 1991).

Network analysis and SEM both aim to explain the variance-covariance structure of high-dimensional data statistically, by comparing a model-implied variance-covariance matrix to the variance-covariance structure of the sample at hand (Bauldry, 2015; Epskamp & Fried, 2018). However, network models do not require assumptions about the underlying data-generating mechanism (Epskamp, Waldorp, et al., 2018). Factor models, conversely, typically specify directional relationships between variables (e.g., identifying predictors in a linear regression). Conceptually, factor models frequently aim to test a priori hypotheses, while networks are primarily an exploratory approach. Notable

exceptions include exploratory uses of factor models, such as exploratory factor analysis (EFA), and recent developments that allow network models to be applied in a confirmatory way (Epskamp, 2020).

Crucially, neither factor models nor network models provide conclusive evidence in favour of a specific data-generating mechanism. Indeed, data generated by a 'true' underlying network can be explained equally well by a factor model and vice versa (Aristodemou et al., 2024). Therefore, in this thesis, I use a combination of SEM and network analysis to model individual symptoms, leveraging each method's strengths, depending on the research question under consideration.

1.3.6 Section summary

Network theory conceptualises mental health disorders as interacting and co-occurring symptoms, rather than latent, unmeasurable constructs. Network analysis provides a statistical framework for the analysis of individual symptoms and their relationships. Other methods, such as structural equation modelling, can also be adapted to model symptoms. In this thesis, I adopt a symptom-level approach to psychopathology, combining network analysis and structural equation modelling.

1.4 Thesis outline

This thesis focuses on individual symptoms of mental health disorders, particularly those associated with depression and anxiety. Broadly, it examines how adopting a symptom-level, dimensional approach can enhance our

understanding of the genetic aetiology (Chapter 2), intermediate mechanisms (Chapter 3), and treatment (Chapter 4) of depression and anxiety (**Figure 1.3**).

Specifically, Chapter 2 investigates the association between genetic risk and individual symptoms of psychopathology in childhood. Using a large sample of 11-year-old children (N=5,521) from the Avon Longitudinal Study of Parents and Children (ALSPAC), I combine PGSs for psychiatry-relevant traits (depression, anxiety, ADHD, educational attainment and BMI) and cross-sectional network analysis to uncover patterns of associations between genetic risk and emotional and behavioural difficulties in childhood. Following a pre-registered confirmatory analysis, primary findings are replicated in an independent sample of children (N=4,625) from the Twins Early Development Study (TEDS).

Chapter 3 extends the above analysis to adults, and combines brain phenotypes, genetic data, and symptoms. In a large sample of adults from the UK Biobank (N=17,823), I examine the associations between genetic risk, regional brain volumes, and symptoms of depression and anxiety. This chapter uses a mediation approach to assess whether regional brain volumes mediate the relationship between PGSs for mental health disorders (depression, ADHD, schizophrenia and bipolar disorder) and individual symptoms.

Chapter 4 examines the effects of pharmacological treatment on symptoms of depression and anxiety. Using data from the PANDA randomised controlled trial (“What are the indications for Prescribing ANtiDepressAnts that will lead to a clinical benefit?”) (N=653), I investigate the effects of the SSRI

sertraline on individual symptoms and their associations. This analysis involves estimating symptom networks at individual time points and applying a cross-lagged panel model to assess longitudinal associations.

Finally, Chapter 5 concludes the thesis by summarising its findings, discussing their implications for mental health research and clinical practice, and addressing key limitations.

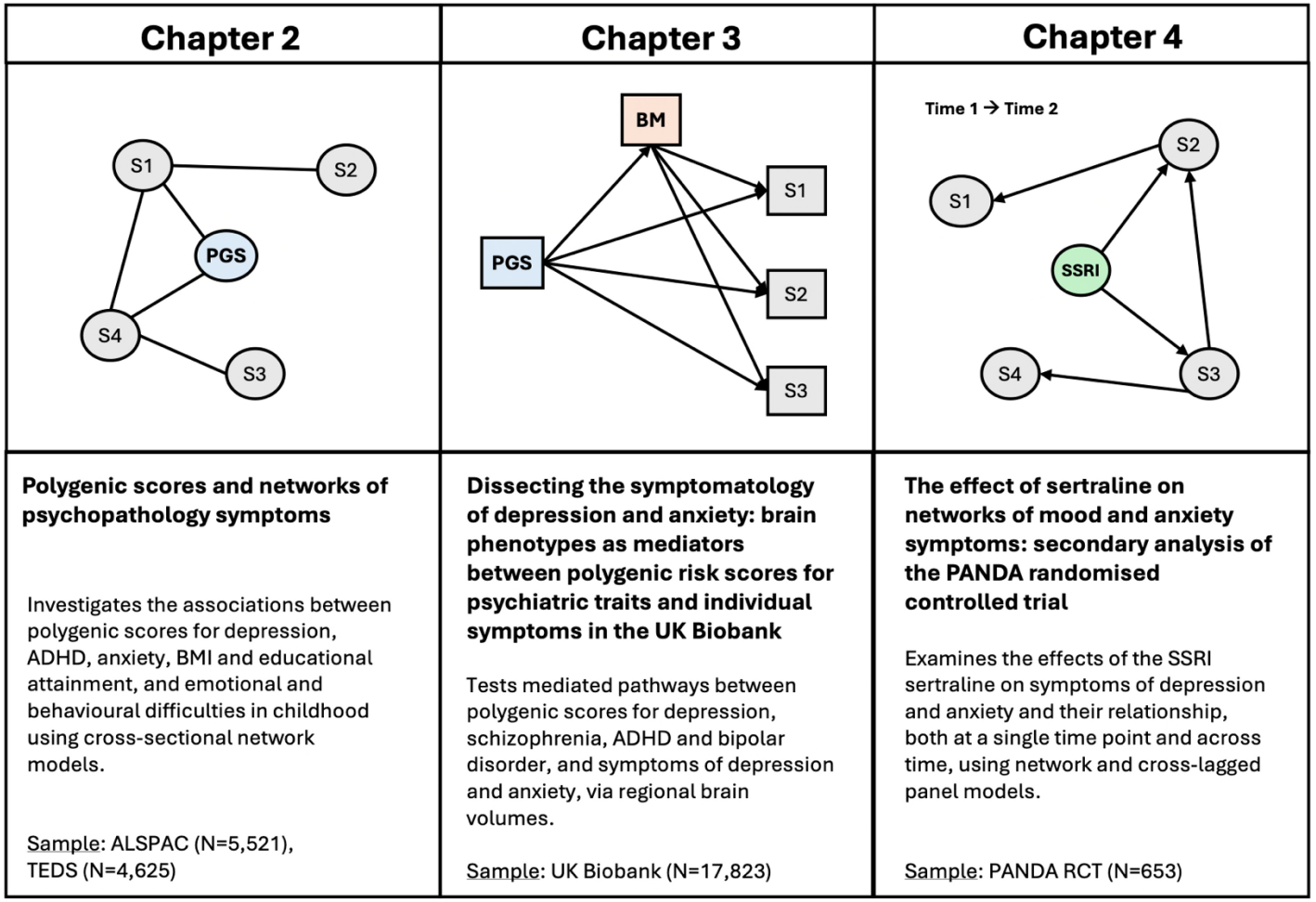


Figure 1.3: Structure and content of the empirical chapters of the thesis.

PGS = polygenic score; BM = brain mediator; SSRI = selective serotonin reuptake inhibitor; S = symptom.

Chapter 2: Polygenic Influences On Networks Of Psychopathology Symptoms

2.1 Abstract

Studies on polygenic risk for psychiatric traits commonly employ a disorder-level approach to phenotyping, implicitly considering disorders as homogenous constructs. However, symptom heterogeneity is ubiquitous, with many possible combinations of symptoms falling under the same disorder umbrella. Focusing on individual symptoms may shed light on the role of polygenic risk in psychopathology. This study aims to determine (i) whether polygenic scores associate with all symptoms of psychiatric disorders, or with a subset of indicators and (ii) whether polygenic scores associate with comorbid phenotypes via specific sets of relevant symptoms.

Data from two population-based cohort studies were used in the study. Data from children in the Avon Longitudinal Study of Parents and Children (ALSPAC) were included in the primary analysis, and data from children in the Twins Early Development Study (TEDS) were included in confirmatory analyses. Data analysis was conducted from October 2021 to January 2024. Pregnant women based in the Southwest of England due to deliver in 1991-1992 were recruited in ALSPAC. Twins born in 1994-1996 were recruited in TEDS from population-based records. Participants with available genetic data and whose mothers completed the Short Mood and Feelings Questionnaire and the Strength and Difficulties Questionnaire when children were 11 years of age were included.

The main outcomes and measures were psychopathology-relevant symptoms, such as hyperactivity, pro-sociality, depression, anxiety and peer and conduct problems at 11 years of age. Psychological networks were constructed including individual symptoms and polygenic scores for depression, anxiety, attention deficit-hyperactivity disorder (ADHD), Body Mass Index (BMI) and educational attainment (EA) in ALSPAC. Following a preregistered confirmatory analysis, network models were cross-validated in TEDS.

I included 5,521 participants from ALSPAC (50.3% female) and 4,625 participants from TEDS (53.2% female). Polygenic scores associate preferentially with restricted subsets of core symptoms and indirectly associate with other, more distal symptoms of psychopathology (network edges range between r=-0.074 and r=0.073). Psychiatric polygenic scores associate with specific cross-disorder symptoms, and non-psychiatric polygenic scores associate with a variety of indicators across disorders, suggesting a contribution of non-psychiatric traits to comorbidity. For example, the polygenic score for ADHD associates with a core ADHD symptom, being easily distracted (r=0.07), and the polygenic score for BMI associates with symptoms across disorders, including being bullied (r=0.053), and not thinking things out (r=0.041).

Genetic associations observed at the disorder level may hide symptom-level heterogeneity. A symptom-level approach may enable a better understanding of the role of polygenic risk in shaping psychopathology and comorbidity.

2.2 Introduction

Genetic studies have consistently shown that many genetic variants, each exerting a small effect, are involved in complex human traits, and together contribute to the likelihood of developing psychiatric disorders (Plomin et al., 2009). This polygenicity can be leveraged to compute polygenic scores (PGSs), weighted sums of risk variants carried by an individual (Allegrini et al., 2022; Janssens et al., 2006). PGSs are a useful research tool indexing the genetic propensity to develop a particular psychiatric disorder, and have become instrumental in investigating the relationship between polygenic risk and psychiatric traits.

Findings based on PGSs partly depend on the operationalisation of heterogeneous phenotypes. Notably, psychiatric disorders include a broad variety of symptoms, which, in combination, lead to numerous clinical presentations. This heterogeneity in psychiatric symptoms may bias genetic findings (N. Cai, Revez, et al., 2020). In fact, evidence shows that symptoms have different heritability estimates, with some genetic effects specific to individual symptoms (Hannigan et al., 2021; Thorp et al., 2020, 2021). Similarly, symptoms are differentially impacted by environmental risk factors and treatment, and contribute differently to relapse risk (Fried et al., 2014; Jang et al., 2004; Rouquette et al., 2018). In addition, some frequently comorbid disorders share a number of symptoms. For example, depression and anxiety frequently co-occur, and both feature insomnia, concentration problems and fatigue (Borsboom, 2002). Findings on the shared genetic liability between comorbid disorders may therefore partly reflect a shared

liability to transdiagnostic disorder features, such as endophenotypes or shared symptoms.

Therefore, analysing unidimensional phenotypes, such as symptoms, can be more informative in uncovering relationships between biology and psychopathology (Tiego et al., 2023) by better capturing the heterogeneity of psychiatric traits (Sluis et al., 2010). Psychological network modelling is a recently developed statistical framework used to examine relationships between individual symptoms (Epskamp, 2020). Modelling observed variables as nodes (e.g., individual items on psychological scales), and their statistical associations as edges (e.g., partial correlations), networks allow for the visualisation of reciprocal dependencies between symptoms, as well as exploratory and confirmatory analyses (Borsboom et al., 2021). By focusing on a more granular, symptom-based phenotype, incorporating PGSs in psychopathology networks can show whether PGSs broadly associate with all facets of a trait or relate specifically to a restricted set of symptoms, and whether PGSs are associated with comorbid disorders via individual symptoms.

Here, I aimed to investigate how polygenic risk for psychopathology-related traits associates with individual symptoms of childhood psychopathology. Firstly, I examined the network structure of childhood behavioural and emotional symptoms, in combination with PGSs for depression, anxiety, ADHD, as well as Body Mass Index (BMI) and Educational Attainment (EA). Secondly, I tested how well the initial exploratory

findings replicated in an independent sample with a preregistered confirmatory network analysis.

2.3 Methods

2.3.1 Sample

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a large birth cohort study based in the Southwest of England which includes data on mothers, fathers, and children (Boyd et al., 2013; Fraser et al., 2013). Pregnant women residing in Avon and expected to deliver between 1991 and 1992 were recruited in the core sample (N=14,541), followed by additional recruitment waves adding 906 pregnancies (14,901 children alive at 1 year of age). Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Informed consent was obtained following the recommendations of the ALSPAC Ethics and Law Committee. The study website contains details of data that is available through a fully searchable data dictionary.

For primary analyses, a sample of children with available genome-wide data was selected (N=8,365). Genotyping, imputation, and quality control steps for ALSPAC data are detailed in Appendix A (Supplementary Methods). Questionnaires sent out when children were 11 years old were selected (N_{ALSPAC}=5,521, 50.3% female, mean age 11.8 years old).

For replication analyses, a sample was selected from the Twins Early Development Study (TEDS), a large UK-based longitudinal study of families of twins born between 1994 and 1996 (N=13,732) (Rimfeld et al., 2019). Identical selection steps were followed to match ALSPAC (N_{TEDS}=4,625, 53.2% female, mean age 11.27 years old). Information on TEDS quality control is detailed by Selzam and colleagues (Selzam et al., 2018).

In both cohorts, only genotyped participants whose mothers responded to at least 75% of questionnaire items were included in the final analytical sample, retaining N=5,521 ALSPAC children and N=4,625 TEDS children out of the initial cohorts. Among these included individuals, I imputed remaining missing items using multiple imputation by predictive mean matching via the R package *mice* (version 3.14.0) (Buuren & Groothuis-Oudshoorn, 2011). Of the maximum possible number of item data points (number of items x number of individuals), I imputed 0.73% of data points that were missing in ALSPAC and 0.1% in TEDS.

2.3.2 Measures

2.3.2.1 Questionnaires

Mother-rated reports of the Short Mood and Feelings Questionnaire (SMFQ, 13 items) and the Strength and Difficulties Questionnaire (SDQ, 25 items) were available in both ALSPAC and TEDS and were selected (Goodman, 2001; Muris et al., 2003). Both are reliable and valid measures of, respectively, depression symptoms and social and emotional well-being, rated on a 3-point scale, 0 (“Not true”), 1 (“Sometimes”), or 2 (“True”). The SDQ is divided into five subscales: ‘Emotional problems’, ‘Peer problems’, ‘Hyperactivity’, ‘Conduct problems’ and ‘Pro-sociality’. Following scoring guidelines, five SDQ items were reverse coded (Items 7, 11, 14, 21, 25). Appendix A (Supplementary Table 1) contains mean values and endorsement rates of SDQ and SMFQ (hereafter referred to as scale items). Items 1 and 4 of the SMFQ (“Miserable/unhappy” and “Restless”) were not present in TEDS and

were therefore excluded in ALSPAC to match datasets, leaving 11 items of the SMFQ in the analysis.

2.3.3 Statistical analyses

All analyses were carried out with R version 4.2.0, outlined in **Figure 2.1** (R Core Team, 2022; von Elm et al., 2007). Example code is available on GitHub. High resolution plots and figures for this Chapter are available online.

2.3.3.1 PGSs calculation

PGSs for depression (based on GWASs summary statistics) (Howard et al., 2019), anxiety (Purves et al., 2020), ADHD (Demontis et al., 2019), BMI (Yengo et al., 2018), and EA (Lee et al., 2018) were calculated using LDPred2 in both cohorts (Privé et al., 2020). To ensure no overlap between target and base data, I selected summary statistics from large GWASs that did not include ALSPAC and/or TEDS in their samples. PGSs were generated by using the option 'LDPred2-auto' with default parameters (using the R package *bigsnpr* version 1.10.8) (Privé et al., 2018), limited to HapMap3 variants (*HapMap 3 - Wellcome Sanger Institute*, 2023) and using target data as reference Linkage Disequilibrium (LD) panels. Recommended quality control steps on GWASs summary statistics were performed prior to generating the scores (Choi et al., 2020) (Appendix A Supplementary Methods).

2.3.3.2 Covariates

To adjust for the effects of covariates on symptoms, age- and sex-regressed standardised residuals for each symptom were obtained from linear regressions and used as input data for networks in both cohorts. Scale items

were adjusted for child age (around 11 years old) and sex. PGSs were adjusted for the first 10 genetic principal components, child age, sex, and genotyping chip and batch.

2.3.3.3 Exploratory network estimation (N≈5,521)

Five cross-sectional networks with scale items and an individual PGSs were estimated in ALSPAC (either depression, anxiety, ADHD, BMI or EA). Additional networks with all PGSs and scale items and scale items only are available in the supplementary material (Appendix A, Supplementary Figure 3).

Unregularised model search was used for network estimation via the R package *qgraph* (version 1.9.2) and its 'ggmModSelect' function (Epskamp et al., 2012), shown to perform optimally in large samples (N > 5,000) compared to other network estimation techniques (Isvoranu & Epskamp, 2021) (Appendix A, Supplementary Methods).

The resulting networks were visualised using the Fruchterman-Reingold algorithm (Fruchterman & Reingold, 1991). The accuracy of network parameters was investigated with the R package *bootnet* (version 1.5) (Epskamp & Fried, 2021). One thousand nonparametric bootstraps were calculated for all network edge weights. Network weights matrices are reported in Appendix A (Supplementary Tables 7-13). Additionally, I report covariate-adjusted correlations between PGSs and scale items (i.e., correlations between each PGS and each scale item, only adjusted for covariates but not adjusted for all other relationships between nodes, in contrast with network analyses) in Appendix A (Supplementary Table 14).

2.3.3.4 Confirmatory Network Estimation (N≈4,625)

I conducted a preregistered confirmatory analysis (https://osf.io/7y2g8) using the R package *psychonetrics* (version 0.10) (**Figure 2.1**) (Epskamp, 2020). First, I tested whether the pattern of presence or absence of associations between items (network structure) was replicated in the secondary sample (model 1). Second, I tested whether the estimates of these associations (network edges) were comparable across samples (model 2). Third, I repeated these steps focusing particularly on associations between PGSs and symptoms (models 3-5).

Specifically, in model 1, I assessed how well network structures derived in the primary sample fit in the secondary sample using standard fit indices (Root Mean Square Error of Approximation, RMSEA; Comparative Fit Index, CFI). In model 2, in a combined dataset, I evaluated the fit of a model with equality constraints on network edges across cohorts, i.e., a model in which all ALSPAC and TEDS edges were set to be equal. For example, I extracted the structure of the network with the ADHD PGS derived in ALSPAC and, in model 1, I tested the fit of this structure in TEDS. In model 2, I set all edges in the ADHD PGS network to have equal weights in ALSPAC and TEDS and evaluated model fit.

In model 3, I tested the overall significance of all edges connecting to the PGS node in a combined dataset. First, I estimated a model where all edges connecting the PGS were set to zero (model 3). For example, if the ADHD PGS was connected to items ‘Easily distracted’ and ‘Child cheats’ in primary results, both edges were set to zero. Second, I compared this to the original

model, where these edges were retained as non-zero. In model 4, these steps were repeated on each edge connecting to PGSs. For example, I set the edge connecting the ADHD PGS to item ‘Easily distracted’ to zero and compared this to the original model, which included the non-zero edge. Lastly, in model 5, individual edges connecting to PGSs were free to vary between cohorts. For example, the edge connecting the ADHD PGS to item ‘Easily distracted’ was allowed to freely vary between ALSPAC and TEDS. I compared this to a model where this edge was set to be equal.

P-values were adjusted for multiple comparisons with False Discovery Rate correction (FDR) using the Benjamini-Hochberg method (alpha = 5%) and the R package *stats* (version 4.2.0) in model 4 (34 tests) and model 5 (35 tests) (Benjamini & Hochberg, 1995; R Core Team, 2022).

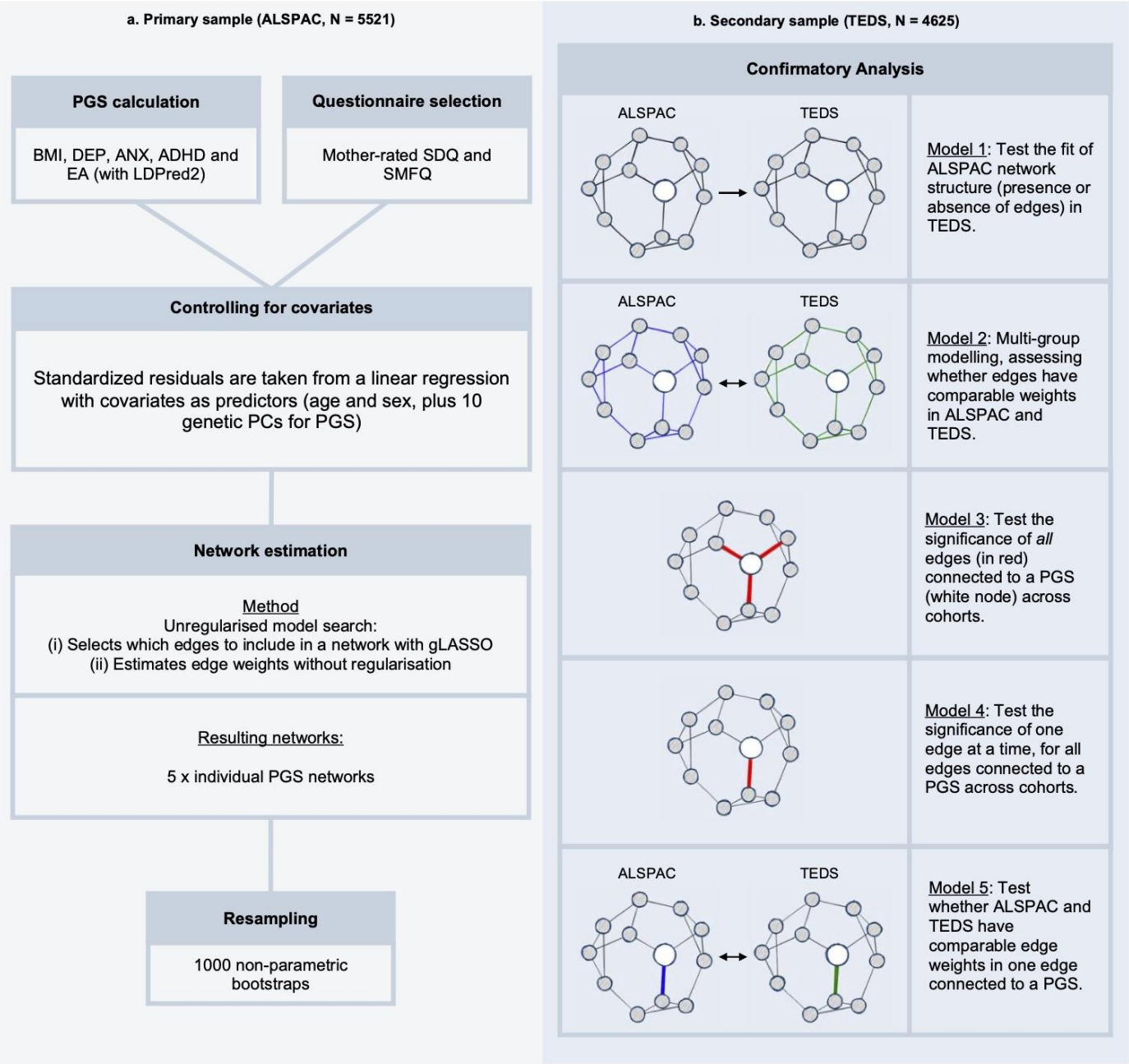


Figure 2.1 (a-b): Analysis flow of the study, including network analysis in ALSPAC (a) and replication in TEDS (b).

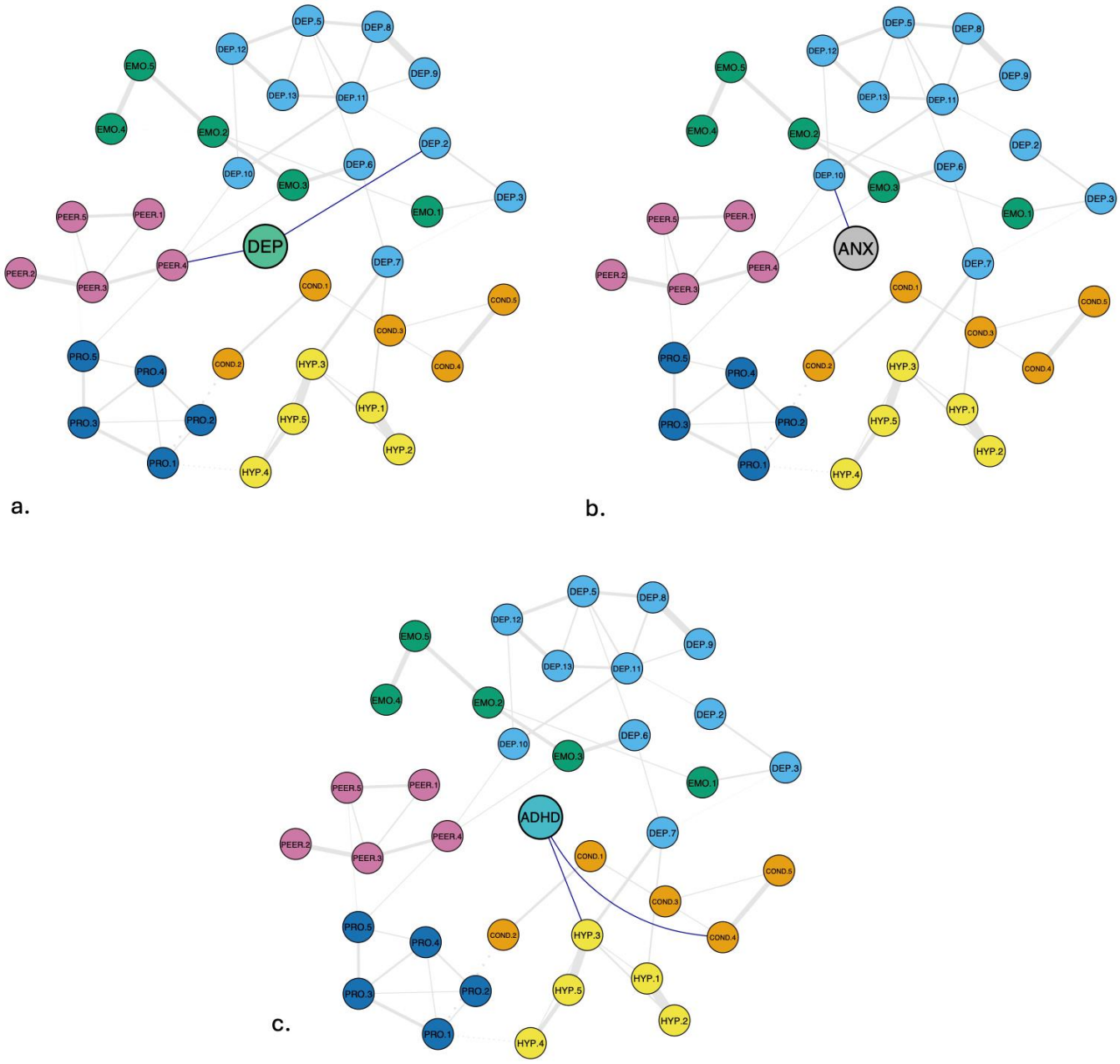
ALSPAC: Avon Longitudinal Study of Parents and Children; TEDS: Twin Early Development Study; PGS: Polygenic Score; BMI: Body Mass Index; DEP: Depression; ANX: Anxiety; ADHD: attention deficit-hyperactivity disorder; EA: educational attainment; SDQ: Strength and Difficulties Questionnaire; SMFQ: Short Mood and Feelings Questionnaire; gLASSO: graphical least absolute shrinkage and selection operator; PC:principal component.

2.4 Results

2.4.1 Exploratory analyses

PGSs preferentially associated with specific items of their corresponding traits (**Figure 2.2**). For example, the ADHD PGS was only associated with one hyperactivity item: 'Easily distracted' (HYP.3) and the depression PGS was associated with depression symptom 'Not enjoying anything' (DEP.2). Additionally, psychiatric PGSs did not associate only with trait-concordant items but showed cross-trait associations. For example, in addition to its within-trait associations, the ADHD PGS also associated with the item 'Child cheats' (COND.4) in the conduct problems subscale, and the depression PGS also associated with 'Being bullied' (PEER.4) in the peer problems subscale. Similarly, the anxiety PGS was associated with depression node 'Feeling lonely' (DEP.10) (**Figure 2.2**). Moreover, PGSs associated with a broader set of items based on covariate-adjusted correlations (i.e. adjusted for covariates, but not adjusted for all relationships between nodes as in network analyses) (Appendix A, Supplementary Table 14).

Lastly, non-psychiatric traits were associated with symptoms across disorders. The BMI PGS (**Figure 2.3**) associated positively with conduct, peer, pro-sociality, and hyperactivity problems and negatively with emotional issues, and the EA PGS negatively associated with items belonging to most subscales, as well as most hyperactivity items (**Figure 2.3**). Nonparametric bootstraps showed edges were estimated accurately, as sample values were comparable to bootstrap mean edge weights (Appendix A, Supplementary Figure 2).



Conduct Problems
COND.1: Temper tantrums
COND.2: Disobedient
COND.3: Often fights
COND.4: Cheats
COND.5: Steals

Peer Problems
PEER.1: Solitary
PEER.2: Does not have a good friend
PEER.3: Not generally liked
PEER.4: Bullied
PEER.5: Gets on better with adults

Depression
DEP.2: Not enjoying anything
DEP.3: Tired
DEP.5: Felt no good
DEP.6: Cried a lot
DEP.7: Hard to concentrate
DEP.8: Hated themselves
DEP.9: Felt like a bad person
DEP.10: Felt lonely
DEP.11: Felt unloved
DEP.12: Felt not as good as others
DEP.13: Felt they did everything wrong

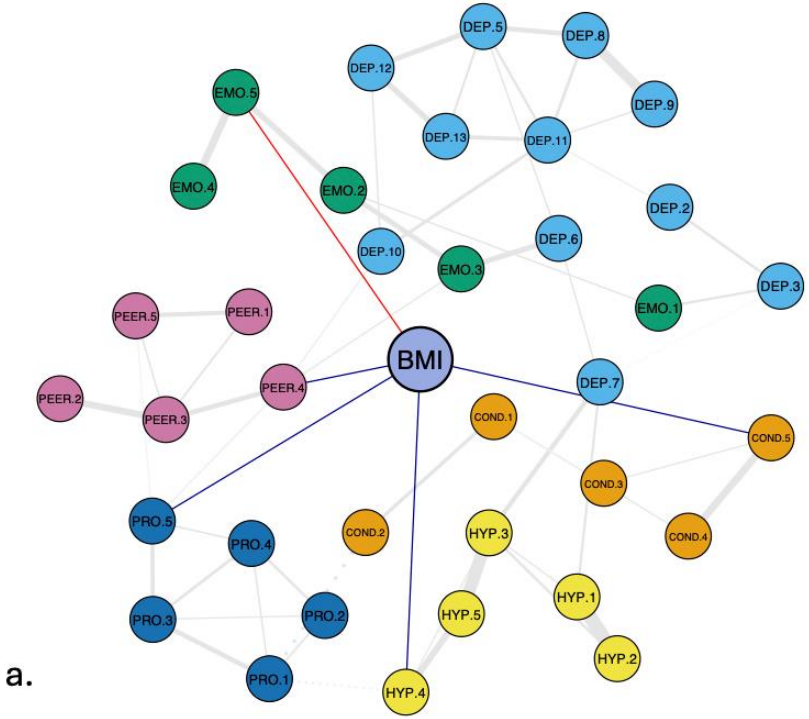
Emotional Problems
EMO.1: Complained of sickness
EMO.2: Many worries
EMO.3: Often unhappy
EMO.4: Nervous in new situations
EMO.5: Many fears

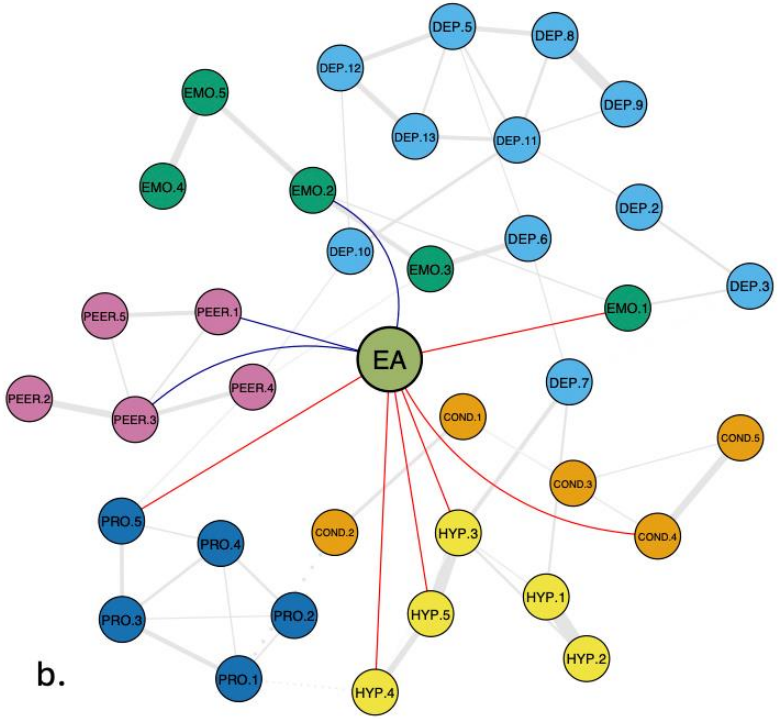
Hyperactivity
HYP.1: Overactive
HYP.2: Fidgeting
HYP.3: Easily distracted
HYP.4: Does not think things out
HYP.5: Bad attention

Prosocial Scale
PRO.1: Considerate of others
PRO.2: Shared readily with others
PRO.3: Helpful
PRO.4: Kind to younger children
PRO.5: Volunteers to help

Polygenic risk scores
DEP: PRS for depression
ANX: PRS for anxiety
ADHD: PRS for ADHD

Figure 2.2 (a-c): Networks of psychiatric polygenic scores and psychopathology symptoms. Plots of networks with depression PGS (a), anxiety PGS (b), ADHD PGS (c). Partial correlations between scale items are drawn in the plot when $|r| > 0.1$ for clarity (i.e., the threshold for *qgraph* visualisation of edges connecting scale items is 0.1). All partial correlations between PGS nodes and scale items are drawn (i.e., *qgraph* visualisation threshold is 0 for edges connecting PGSs). All edges connecting PGSs are blue when positive and red when negative. All edges connecting scale items are solid grey when positive and dotted grey when negative. Bold items in the legend indicate nodes connected to a PGS. PGSs are in the centre of each graph and all other nodes are positioned according to an average layout obtained with the Fruchterman-Reingold algorithm. Appendix A Supplementary Figure 1 includes all networks without thresholds and common layout.





Conduct Problems
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HYP.4: Does not think things out
HYP.5: Bad attention

Prosocial Scale
PRO.1: Considerate of others
PRO.2: Shared readily with others
PRO.3: Helpful
PRO.4: Kind to younger children
PRO.5: Volunteers to help

Polygenic risk scores
EA: PRS for educational attainment
BMI: PRS for BMI

Figure 2.3 (a-b): Networks of non-psychiatric polygenic scores and psychopathology symptoms.

Plots of networks with BMI PGS (a) and EA PGS (b). As in Figure 2.2, partial correlations between scale items are drawn in the plot when $|r| > 0.1$ for clarity, and all partial correlations between PGS nodes and scale items are drawn. All edges connecting PGSs are blue when positive and red when negative. All edges connecting scale items are solid grey when positive and dotted grey when negative. Bold items in the legend indicate nodes connected to a PGS. PGSs are in the centre of each graph and all other nodes are positioned according to an average layout obtained with the Fruchterman-Reingold algorithm.

2.4.2 Confirmatory analyses

Overall, networks replicated well across datasets. Models 1 and 2 indicated network models were successfully replicated in the secondary sample. All network structures derived in ALSPAC showed good model fit in TEDS based on standard fit indices in model 1 (**Table 2.1**). Similarly, when setting equality constraints between ALSPAC and TEDS edges (model 2), model fit was good across all networks (Appendix A, Supplementary Table 3). Although standard fit indices were comparatively better when edges were not constrained to be equal across samples, indices accounting for model complexity (e.g., the Bayesian Information Criterion) consistently favoured models with constrained edges.

Edges connecting PGSs were statistically significant in all networks, as models including these edges (models 3 and 4) fit better than models that excluded them (Appendix A, Supplementary Tables 4-5). In addition, results from model 5 show that PGSs had similar associations with items across cohorts. Models constraining PGS edges to be equal in ALSPAC and TEDS were preferred to models which lifted these equality constraints, except the edge between the EA PGS and item ‘Child cheats’ (COND.4). This difference, however, did not survive corrections for multiple comparisons (**Table 2.2**).

Table 2.1: Model fit indices from model 1, testing the model fit of ALSPAC networks in TEDS.

CFI above 0.95 and RMSEA below 0.05 were considered indicators of good model fit and of successful replication of ALSPAC networks in TEDS. CFI: Comparative Fit Index; RMSEA: Root Mean Square Error of Approximation.

Fit index	ADHD PGS network	Depression PGS network	Anxiety PGS network	EA PGS network	BMI PGS network
CFI	0.977	0.979	0.978	0.978	0.977
RMSEA	0.021	0.020	0.021	0.021	0.021

Table 2.2: Weights (partial correlations) of the edges of interest in PGSs networks. These were derived from primary analyses (ALSPAC weights), confirmatory model 1 (TEDS weights) and confirmatory model 2 (constrained model weights). †: significantly different weight estimates in TEDS and ALSPAC based on uncorrected *p*-values in model 5. When correcting for multiple comparisons, the difference is non-significant. All other estimates are not significantly different in TEDS and ALSPAC based on both uncorrected and corrected *p*-values.

Network and items	Edge	ALSPAC weight	TEDS weight	Constrained model weight
EA PGS network				
Cheats†	COND.4--EA†	-0.049	-0.098	-0.072
Complained of sickness	EMO.1--EA	-0.044	-0.014	-0.031
Many worries	EMO.2--EA	0.040	0.053	0.046
Easily distracted	HYP.3--EA	-0.062	-0.044	-0.054
Does not think things out	HYP.4--EA	-0.052	-0.028	-0.040
Bad attention	HYP.5--EA	-0.048	-0.069	-0.058
Solitary	PEER.1--EA	0.037	0.010	0.025
Not generally liked	PEER.3--EA	0.036	0.027	0.033
Volunteers to help	PRO.5--EA	-0.078	-0.069	-0.074
BMI PGS network				
Steals	COND.5--BMI	0.048	0.039	0.044
Many fears	EMO.5--BMI	-0.039	-0.011	-0.026
Does not think things out	HYP.4--BMI	0.043	0.038	0.041
Bullied	PEER.4--BMI	0.051	0.054	0.053
Volunteers to help	PRO.5--BMI	0.074	0.073	0.073
ADHD PGS network				
Cheats	COND.4--ADHD	0.048	0.040	0.044
Easily distracted	HYP.3--ADHD	0.070	0.069	0.070
Depression PGS network				
Not enjoying anything	DEP.2--DEP	0.037	0.037	0.038
Bullied	PEER.4--DEP	0.055	0.036	0.047
Anxiety PGS network				
Felt lonely	DEP.10--ANX	0.040	0.014	0.028

2.5 Discussion

This study examined the associations between childhood psychopathology symptoms and PGSs for psychiatric disorders and relevant traits using a network approach. I found that (i) psychiatric PGSs are associated with a core subset of indicators of their corresponding traits and (ii) PGSs are not only associated with symptoms of their respective trait but show direct cross-trait associations. These findings were replicated in an independent sample and, as discussed below, suggest that the relationship between (non-)psychiatric polygenic risk and psychopathology traits may be mediated by specific factors or other symptoms.

2.5.1 Trait-relevant associations between PGSs and symptoms

PGSs associated with a selection of items measuring their corresponding trait. For example, the ADHD PGS was only positively associated with one item in the hyperactivity subscale, 'Easily distracted' (HYP.3). This result suggests that the association between ADHD and the polygenic risk for ADHD might be preferentially explained by the association with cognitive-attentional elements of the disorder. Similarly, the depression PGS was associated positively with anhedonia ('Not enjoying anything', DEP.2), suggesting that the polygenic risk for depression might primarily influence prominent features of the disorder, associated with the greatest impairment (Fried & Nesse, 2014). When associations between items and PGSs were not adjusted for all relationships between network nodes (i.e., in covariate-adjusted correlations, Appendix A, Supplementary Table 14), PGSs associated with a broader set of items than those identified by network analysis.

Taken together, these results suggest that associations between PGSs and psychiatric traits might be preferentially explained by the association with core symptoms, rather than reflect uniform associations with all symptoms as commonly implied by disorder-level analyses. These core symptoms may be key mediators in the relationships between PGSs and other, more distal symptoms of psychopathology.

2.5.2 Cross-trait associations between PGSs and symptoms

PGSs for psychiatric disorders were also found to be associated with items that did not directly measure PGS-concordant phenotypes. Notably, the anxiety PGS was associated with depression symptom 'Feeling lonely' (DEP.10). This may indicate that a shared genetic influence on individual symptoms of depression and anxiety contributes to their frequent co-occurrence.

Similarly, the EA PGS was negatively associated with individual hyperactivity items. Previous evidence suggests that higher EA PGS predict lower ADHD symptoms and better inhibitory control (Rea-Sandin et al., 2021). Indeed, networks showed that the EA PGS was negatively associated with cheating (COND.4), having poor attention (HYP.5) and being easily distracted (HYP.3) and impulsive (HYP.5), and also positively associated with internalising and peer problems, such as being solitary (PEER.1), having many worries (EMO.2), not being liked (PEER.3), and not volunteering to help others (PRO.5). This may suggest that childhood EA is a reflection of social and cognitive processes that also play a part in most internalising and externalising disorders.

Furthermore, the BMI and depression PGS associated with peer problems, specifically with being bullied (PEER.4). In turn, being bullied was positively associated with being lonely (DEP.10) and often unhappy (EMO.3), suggesting that being bullied may mediate the relationship between these PGSs and depression symptoms. This is also consistent with recent evidence showing the genetic predisposition to higher BMI, depression and ADHD is associated with bullying victimisation in children (Schoeler et al., 2019). Pre-existing vulnerability to mental illness might lead to exposure to bullying in childhood, which in turn exacerbates emotional difficulties in adolescence (Riglin et al., 2019), hyperactivity and impulsivity, inattention, and conduct problems (Singham et al., 2017). This represents a pattern of evocative gene-environment correlation: children who are predisposed to developing a high BMI might, in some contexts, evoke particular reactions in their environment, such as bullying (Davidson & Demaray, 2007). Unfavourable environments, in turn, affect mental and physical health. This can have cascading effects, as stress in early life mediates the association between the genetic predisposition to high BMI and later depression (Avinun & Hariri, 2019).

In sum, adopting a network approach to phenotyping can suggest potential pathways to developing psychiatric traits by highlighting indirect paths from polygenic risk to later psychopathology via intermediate phenotypes. Taking a dimensional view of psychopathology, this study investigated the extent to which common genetic variation in the population (indexed by PGSs) associates with individual differences in symptoms. Findings should be replicated in high-risk or clinical cohorts.

2.5.3 Limitations

A few limitations of this study merit comment. First, the partial correlations evidenced in this study cannot be assumed to reflect causal mechanisms.

Second, results derived from the discovery cohort (ALSPAC) may be affected by overfitting, which, consequently, could affect results in the combined sample of both cohorts (models 3 and 4). As such, edges between PGSs and scale items derived in the confirmatory sample are the most conservative estimates (**Table 2.2**). Models investigating differences in edges between cohorts (model 5) were implemented to minimise this issue. In fact, no systematic deflation of estimates was observed in the second cohort, reducing the likelihood of inflated estimates in the discovery cohort.

Third, polygenic scoring is a proxy for individual genetic liability, and it does not capture the full heritability of a trait (SNP-heritability) due to measurement error, meaning there are likely associations between genetic liabilities and symptoms that this analysis was not able to detect. The PGSs calculated in this study vary in predictive power, in accordance with the GWASs they were derived from. This may explain some findings, such as the EA PGS associating with more symptoms of ADHD than the ADHD PGS itself.

Lastly, ALSPAC and TEDS are affected by attrition (Boyd et al., 2013; Fraser et al., 2013; Rimfeld et al., 2019). Therefore, replications of these findings in representative cohorts with high retention rates are warranted. Similarly, this analysis was limited to participants of European descent. As more diverse samples are being made available for genetic research, it will be important to verify whether findings hold true in those samples. Replication

studies would also benefit from using more normally distributed item data and more granular genetic data (e.g. symptom-level GWASs, see Appendix A, Supplementary Discussion).

2.5.4 Conclusion

Modelling polygenic risk in networks of psychological variables showed previously unreported patterns of associations that replicated across samples. Relationships between psychopathology-related PGSs and childhood psychological difficulties showed that PGSs are preferentially associated with specific trait-relevant and cross-trait symptoms. Introducing genetic data into psychological networks can provide new insights into the aetiology of comorbidity as well as identify potential pathways to the development of psychiatric traits.

Chapter 3: Dissecting the Symptomatology of Depression and Anxiety: Brain Phenotypes as Mediators Between Polygenic Risk Scores for Psychiatric Traits and Individual Symptoms in the UK Biobank

3.1 Abstract

Brain phenotypes, including structural cortical and subcortical measures, are heritable traits that may mediate the relationship between genetic factors and phenotypic depression. However, studies linking genetic factors and depression via brain morphology have produced mixed results. This may be partly due to the heterogeneity of depression symptoms, many of which overlap with symptoms of comorbid disorders. Neglecting symptom heterogeneity may obscure symptom-specific genetic effects that act through neurobiological mechanisms.

In this study, I examine associations between genetic factors, brain structure, and individual symptoms of depression and anxiety in a large sample from the UK Biobank (N=17,823). Using mediation analyses, I assess whether the volumes of brain regions implicated in depression and commonly comorbid disorders (insula, hippocampus, medial orbitofrontal cortex, fusiform, and cingulate) mediate associations between polygenic scores for depression and commonly comorbid disorders (ADHD, bipolar disorder, and schizophrenia) and individual symptoms of depression and anxiety.

I demonstrate that polygenic scores for disorders comorbid with depression are associated with specific symptoms of depression and anxiety. Notably, although I did not detect associations between regional brain volumes and symptoms when treated as sum-scores, there were clear associations with individual symptoms. Somatic symptoms, such as tiredness, appetite and sleep problems, were robustly associated with both polygenic scores and region brain volumes. However, I find no evidence that structural brain markers mediate the relationships between polygenic scores and individual symptoms.

These results indicate that addressing symptom heterogeneity by focusing on individual symptoms can reveal novel patterns of associations, which have the potential to improve our understanding of depression and its comorbidities.

3.2 Introduction

Depression is a common heritable disorder with a multifactorial causal structure (Otte et al., 2016). Comorbidity is a common feature of depression, which frequently co-occurs with other psychiatric disorders (Caspi et al., 2020; Kessler et al., 2005). Research has identified factors that may explain comorbidity, such as a shared genetic architecture and a shared neural substrate across disorders (Martin et al., 2018; Vanes & Dolan, 2021). However, there have been significant challenges in linking depression to genetic or neurobiological biomarkers, which may be in part due to symptom heterogeneity (Borsboom, 2017; Fried et al., 2014). Therefore, focusing on individual symptoms may offer a better way to capture the pathobiology of depression.

Depression symptoms vary substantially in their origin, clinical presentation, and severity, and a diagnosis of depression can result from hundreds of different symptom combinations (Fried et al., 2020; Fried & Nesse, 2015). Yet, most research operationalises depression as a single dimension, often relying on aggregate scores (e.g., total scores on a scale). Moreover, many symptoms are not specific to depression, but recur across several conditions (American Psychiatric Association, 2013), including those that frequently co-occur with depression (Forbes et al., 2023). Consequently, comorbidity may partly reflect overlapping symptoms. Symptom overlap may impede efforts to investigate factors that contribute to psychiatric comorbidities (Forbes, 2023), such as shared genetic and neurobiological pathways.

Genetic studies consistently show that depression is a polygenic trait, influenced by many genetic variants with small effect sizes (Howard, 2019; Plomin et al., 2009; Wray et al., 2018). Notably, individual depression symptoms may be differentially heritable and associated with distinct genetic variants (Thorp et al., 2020, 2021). Studies using polygenic scores (PGSs), which index an individual's genetic propensity for a particular trait (Allegrini et al., 2022), show that the polygenic risk for depression is associated with individual symptoms of depression and with symptoms of comorbid disorders (Bjørndal et al., 2024; Piazza et al., 2024), suggesting that a symptom-level approach can reveal insights into the complex genetic nature of comorbidity.

Much like psychiatric disorders, brain phenotypes have complex polygenic architectures, and may be closer to gene activity than other phenotypic measures, such as behaviour (Buch & Liston, 2021). In particular, morphological brain measures, such as regional volumes, are heritable (den Braber et al., 2013; Elliott et al., 2018) and associated with psychiatric disorders (Arnone et al., 2012; Gray et al., 2020; Holmes et al., 2012; Thompson et al., 2021). Meta-analytic results from the large-scale collaborative initiative Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) show that reduced cortical and subcortical volumes in regions such as the hippocampus, cingulate, fusiform and orbitofrontal cortex distinguish depressed patients and healthy controls (Schmaal et al., 2016, 2017, 2020), albeit with modest effect sizes.

Additionally, neuroimaging studies provide evidence of transdiagnostic brain markers, such as shared patterns of altered brain structure across

disorders (Brosch et al., 2022; Goodkind et al., 2015; McCutcheon et al., 2023; Vanes & Dolan, 2021; Wise et al., 2017). Notably, recent studies have linked individual depression symptoms to specific brain volumes, suggesting, for example, that hippocampus size is associated with anhedonia, sadness, irritability, and appetite problems (Freichel et al., 2024; Hilland et al., 2020). Therefore, symptoms may arise from distinct brain pathways, and symptom overlap may lead to an overestimation of the similarities of brain alterations across disorders.

A few studies have begun to examine whether brain measures mediate the association between PGSs for depression and depression symptomatology, but findings to date are largely inconclusive. For example, some studies found no evidence of an association between the PGS for depression and subcortical volumes in the first release of the UK Biobank (UKB) imaging data (Reus et al., 2017) and in a sample drawn from Generation R (Alemany et al., 2019). Another study found an association between the depression PGS and both increased and decreased regional grey matter volumes in a sample of the Human Connectome Project (Fu et al., 2024). Fu and colleagues also reported that the right cerebellum crus I grey matter volume mediated the association between the PGS for depression and depression severity. These contradictory findings may partly reflect symptom heterogeneity, as distinct neural and genetic mechanisms may underlie individual depression symptoms.

In summary, aggregating non-specific and heterogeneous symptoms may impact our understanding of genetic risk and brain phenotypes, and

consequently bias research into comorbidity in depression. To date, no study has adopted a symptom-level perspective to account for symptom heterogeneity when investigating the relationship between genetic factors, brain phenotypes and behaviour. Therefore, I aimed to link genetic, neuroimaging, and individual symptom measures to reveal patterns of associations across levels of organisation. In a sample from the UKB, I investigated whether polygenic risk scores for depression and comorbid disorders (attention deficit-hyperactivity disorder or ADHD, bipolar disorder and schizophrenia) are associated with (i) individual symptoms of depression and anxiety and (ii) volumes of brain regions implicated in depression. I further aimed to (iii) investigate associations between regional brain volumes and individual symptoms and (iv) test whether brain volumes mediate the relationship between polygenic scores and individual symptoms.

3.3 Methods

3.3.1 Sample

The UKB is a large population-based cohort study that includes 502,185 participants and a wide range of biomedical and lifestyle data. I included Caucasian participants who underwent a brain MRI scan (in the first imaging visit in the UK Biobank, conducted from 2014), provided T1 structural brain images, and genetic and mental health data. The study was approved by the UKB's research ethics committee, and the current analysis was approved under project 29819.

3.3.2 Measures

3.3.2.1 Genetic measures

I selected ADHD, schizophrenia and bipolar disorder, in addition to depression, as these traits (i) share at least one symptom with depression based on symptoms reported in the DSM (DSM-5, American Psychiatric Association, 2013), (ii) show alterations in brain structures implicated in depression, based on comparisons with healthy controls reported in ENIGMA meta-analyses (Opel et al., 2020), and (iii) are genetically correlated with depression (Martin et al., 2018).

I excluded genetic samples identified by the UKB as outliers in heterozygosity and missing rates and participants with genetic kinship to other UKB participants. I applied quality control procedures to genotype data, excluding variants with Minor Allele Frequency (MAF) below 0.01 and those violating Hardy Weinberg's equilibrium (p < 1e-06). I excluded samples with

missing variant and per-sample call rates exceeding 0.01 and duplicate variants (Choi et al., 2020).

I used summary statistics derived from samples of published genome-wide association studies (GWASs) that did not include the UKB to ensure independence between base and target data for PGS calculations (depression, Wray et al., 2018; schizophrenia, Trubetskoy et al., 2022; bipolar disorder, Mullins et al., 2021; ADHD, Demontis et al., 2023). In quality control for summary statistics, I excluded non-autosomal variants, removed variants with imputed information scores (INFO) below 0.8 and MAF below 0.01 (when provided), and removed ambiguous and duplicate variants (Choi et al., 2020).

3.3.2.2 Brain measures

I included UKB's imaging-derived phenotypes (IDPs) to describe regional brain volumes. I included volumes of brain regions estimated using FreeSurfer from T1 structural images and averaged over the left and right hemispheres. More details on image acquisition, processing and derivation of IDPs are reported in the UKB's online brain imaging documentation and published literature (Alfaro-Almagro et al., 2018; Miller et al., 2016; Smith et al., UK Biobank online documentation). I included regional brain volumes that showed the largest case-control differences in studies from the ENIGMA depression working group (Schmaal et al., 2020) – the medial orbitofrontal cortex (mOFC), fusiform gyrus, insula, hippocampus and cingulate (an average of the rostral anterior cingulate and caudal anterior cingulate). IDPs were scaled to have a mean of 0 and a standard deviation of 1.

3.3.2.3 Mental health measures

I included sixteen individual symptoms of anxiety and depression from the UKB's mental health web-based questionnaire completed by participants before August 2017, which was based on the Patient Health Questionnaire (PHQ-9) and Generalised Anxiety Disorder Questionnaire (GAD-7). Participants rated questions on recent symptoms of depression and anxiety ("Over the last two weeks, how often have you been bothered by any of the following problems?") on a scale from 0 ('Not at all') to 3 ('Nearly every day').

3.3.3 Statistical analyses

Analyses were carried out using the UKB's Research Analysis Platform through the R Studio App (R version 4.4.0) (R Core Team) (**Figure 3.1**). PLINK (Purcell et al., 2007) was used to conduct quality control on genetic data. The code used in the analyses is available on GitHub. High resolution plots and figures for this Chapter are available online.

3.3.3.1 Calculation of PGSs

PGSs for ADHD, schizophrenia, depression and bipolar disorder were derived using LDPred2 and its -auto option (Privé et al., 2020) with default parameters, using the R package *bigsnpr* (version 1.12.15) (Privé et al., 2018). Variants were limited to HapMap3 (HapMap 3 - Wellcome Sanger Institute), and the UKB was used as a reference Linkage Disequilibrium (LD) panel.

3.3.3.2 Missing data and multiple imputation

After selecting participants with complete genetic and IDP data, the maximum percentage of missing values across the remaining variables (item-level questionnaire data) was 23.72%, while the maximum percentage of missing values across cases was 22.38%. I thus imputed the mental health questionnaire data (16 depression and anxiety symptoms from the UKB's mental health web-based questionnaire, based on PHQ-9 and GAD-7). I imputed 25 datasets (more than the percentage of incomplete cases, as suggested in White et al., 2011) with predictive mean matching using the R package *mice* (version 3.16.0) (Buuren & Groothuis-Oudshoorn, 2011). All data in the selected sample (genetic measures, mental health measures, brain measures, age and sex) were included in the multiple imputation procedure.

3.3.3.3 Mediation analysis

I used the R package *lavaan.mi* (version 0.1-0.003) (Terrence, 2024) to fit mediation models to the 25 imputed datasets. To accurately model categorical data and mitigate the impact of skewness, I used weighted least square mean and variance adjusted (WLSMV) estimation and robust standard errors.

First, I estimated four mediation models with a single PGS ("*Single PGS*" models). That is, for each PGS (separately, either ADHD, schizophrenia, depression or bipolar disorder PGS), I estimated a model with sixteen symptom outcomes (depression and anxiety symptoms) and five brain mediators (mOFC, cingulate, insula, hippocampus and fusiform gyrus). Second, I estimated a mediation model with all four PGSs, sixteen symptom outcomes and five brain mediators ("*Multiple PGSs*" model) (**Figure 3.2**).

Rubin's rules (Rubin, 1987) were used to pool point estimates and standard errors and calculate degrees of freedom, *p*-values and confidence intervals across imputed datasets (using *lavaan.mi*). In all models, sex, age, and ten genetic principal components were added as covariates when estimating associations between PGSs, brain mediators and symptom outcomes.

In 'Single PGS' and 'Multiple PGSs' models, I estimated both individual and total mediation effects. For example, I estimated how much of the association between the depression PGS and the symptom 'Tiredness' was mediated by the volume of the fusiform gyrus (individual mediation effect). I also estimated how much of this association was mediated by any brain mediator (summing the effects through all brain areas; total mediation effect).

In sum, each mediation model estimated the unmediated effects from PGSs to symptoms (e.g., 'c1.1' in **Figure 3.2**), paths from PGSs to brain mediators (e.g., 'a1.1'), paths from brain mediators to symptoms (e.g., 'b1.1'), individual mediation effects (e.g., 'a1.1*b1.1'), and total mediation effects (e.g., 'a1.1*b1.1 + … + a1.5*b5.1') and total paths from PGSs to symptoms (sums of mediated and unmediated effects, e.g., 'a1.1*b1.1 + c1.1').

3.3.3.4 Secondary analyses

I estimated two additional mediation models with all four PGSs, five brain mediators and total score outcomes derived from symptom-level data (in one model, either a depression or an anxiety total score) ('*Total score'* models). I also estimated simple correlations between PGSs, brain measures and symptoms using the R package *miceadds* (version 3.17-44) (Alexander Robitzsch et al., 2024).

3.3.3.5 Adjustments for multiple comparisons

P-values were adjusted for multiple comparisons with False Discovery Rate (FDR) correction using the Benjamini-Hochberg method (alpha=5%) (Benjamini & Hochberg, 1995) and the R package *stats* (version 4.2.0) (R Core Team), based on the number of tests conducted in each analysis. For example, in mediation analyses, each *p*-value for total paths was corrected for the overall number of total paths (e.g., 64 paths in the 'Multiple PGSs' model, given 16 symptom outcomes and 4 PGSs). Similarly, each *p*-value of the associations between PGSs, brain mediators, and symptoms – 'a', 'b', and 'c' paths in **Figure 3.2** – was corrected for the sum of 'a', 'b', and 'c' paths (e.g., 20 'a' paths, 80 'b' paths, 64 'c' paths, totalling 164, in the 'Multiple PGSs' model). Each *p*-value for individual and total mediation effects was corrected for the overall number of individual and total mediation effects respectively (e.g., 320 individual and 64 total mediation effects in the 'Multiple PGSs' model).

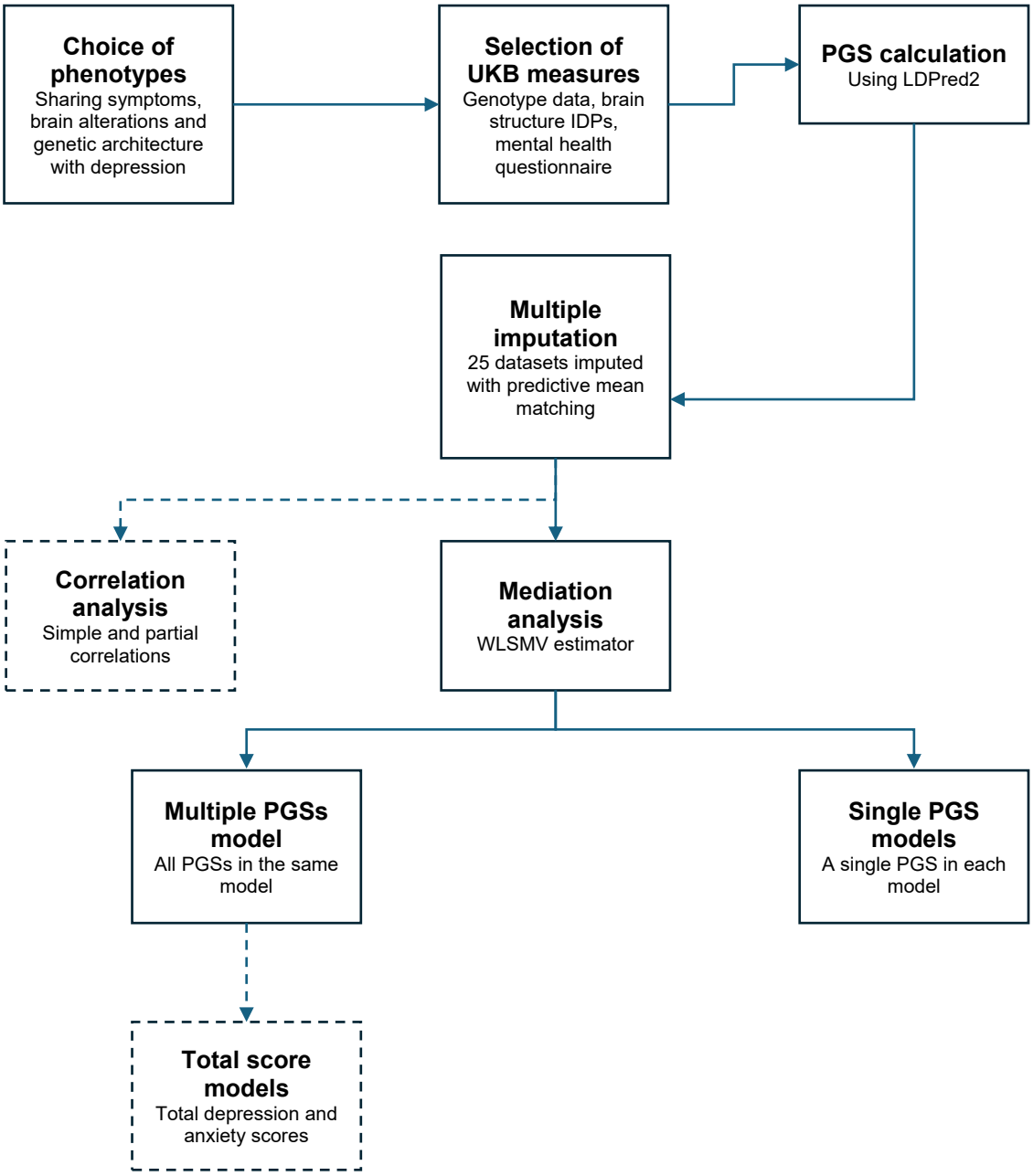


Figure 3.1: Analysis flow of the study.

Solid lines indicate main analyses, and dotted lines indicate secondary ones. PGS = polygenic score; WLSMV = weighted least square mean and variance adjusted.

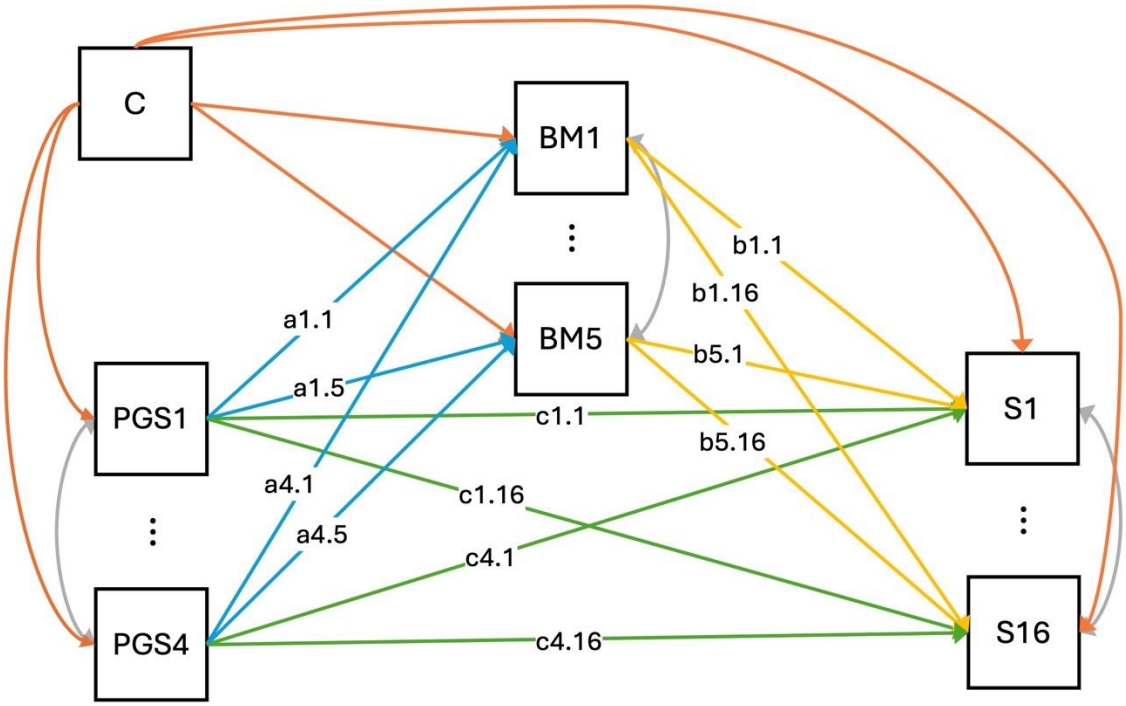


Figure 3.2: Schematic representation of the multiple PGSs mediation model.
The representation visualises unmediated effects from PGSs to symptoms ('c' paths in green), associations between PGSs and brain mediators ('a' paths in blue), and between brain mediators and symptoms ('b' paths in yellow). Associations between covariates, PGSs, brain mediators and symptoms are represented by orange arrows, and covariances between PGSs, symptoms and brain mediators are represented by grey double arrows. The full model includes 4 PGSs, 5 brain mediators, 16 outcomes and 12 covariates (sex, age, and 10 genetic principal components). PGS = polygenic score; BM = brain mediator; S = symptom; C = covariates.

3.4 Results

A total of 17,823 participants with neuroimaging data passed genetic quality control. Demographic information means and standard deviations of the variables of interest in imputed and non-imputed data are displayed in **Table 3.1**.

Table 3.1: Description of the sample in Chapter 3.
Sample size (N) for each variable of interest, abbreviations, means and standard deviations (SDs) of age, depression and anxiety questionnaire items and total scores in imputed and non-imputed data. Means and SDs of imputed data were averaged across 25 imputed datasets.

		Non-imputed data		Imputed data (25 datasets, N = 17823)
		N	**Mean (SD)**	**Mean (SD)**
	Sex	17823 total 9217 (51.7%) females	-	-
	Age	17823	55.17 (7.45)	-
Abbreviation	**Depression**			
PSY	*Psychomotor issues*	13725	0.06 (0.32)	0.06 (0.31)
DEP	*Depressed*	13699	0.26 (0.55)	0.25 (0.53)
INA	*Feeling inadequate*	13675	0.22 (0.56)	0.22 (0.55)
TIR	*Tired*	13711	0.62 (0.81)	0.62 (0.80)
INT	*Lack of interest*	13710	0.24 (1.56)	0.23 (0.55)
APP	*Appetite problems*	13724	0.23 (0.60)	0.22 (0.59)
SUI	*Suicidal thoughts*	13647	0.04 (0.26)	0.04 (0.25)
CON	*Concentration problems*	13723	0.23 (0.55)	0.22 (0.54)
SLE	*Sleep problems*	13707	0.69 (0.90)	0.68 (0.89)
TOT.D	*Total score*	13520	2.54 (3.52)	2.55 (3.46)
	Anxiety			
ANX	*Anxious*	13616	0.32 (0.60)	0.31 (0.59)
WOR	*Can't control worry*	13611	0.28 (0.60)	0.28 (0.59)
WOR.T	*Worrying too much*	13606	0.37 (0.64)	0.36 (0.62)
REL	*Trouble relaxing*	13616	0.31 (0.63)	0.31 (0.62)
RES	*Restless*	13623	0.12 (0.42)	0.12 (0.41)
IRR	*Irritable*	13596	0.28 (0.55)	0.28 (0.54)
FORE	*Sense of foreboding*	13597	0.21 (0.53)	0.20 (0.52)
TOT.A	*Total score*	13508	1.88 (3.12)	1.87 (3.04)

3.4.1 Total effects of polygenic scores on individual symptoms

All PGSs were significantly associated with the majority of symptoms of depression and anxiety in the 'Single PGS' models (Appendix B, Supplementary Table 1). However, in the 'Multiple PGSs' model, only the depression PGS was significantly positively associated with all symptoms (ranging from sleep problems, $\beta_{DEP\ PGS\text{-}SLE}$=0.036, 95%CI [0.016, 0.056], p_{FDR}<0.001, to tiredness, $\beta_{DEP\ PGS\text{-}TIR}$= 0.064, 95%CI [0.044, 0.085], p_{FDR}<0.001) (**Figure 3.3**). The ADHD PGS was significantly associated with a subgroup of symptoms (ranging from sleep problems, $\beta_{ADHD\ PGS\text{-}SLE}$=0.026, 95%CI [0.007, 0.046], p_{FDR}=.027, to appetite problems, $\beta_{ADHD\ PGS\text{-}APP}$= 0.066, 95%CI [0.042, 0.091], p_{FDR}<0.001), and the schizophrenia PGS was associated with appetite problems ($\beta_{SCZ\ PGS\text{-}APP}$=0.04, 95%CI [0.014, 0.066], p_{FDR}=.010).

Total depression scores were associated with depression, ADHD and schizophrenia PGSs ($\beta_{DEP\ PGS\text{-}TOT.D}$=0.054, 95%CI [0.038, 0.070], p_{FDR}<0.001; $\beta_{ADHD\ PGS\text{-}TOT.D}$=0.041, 95%CI [0.041, 0.057], p_{FDR}<0.001; $\beta_{SCZ\ PGS\text{-}TOT.D}$=0.018, 95%CI [0.002, 0.035], p_{FDR}=.034), and total anxiety scores were associated with depression and ADHD PGSs ($\beta_{DEP\ PGS\text{-}TOT.A}$=0.044, 95%CI [0.028, 0.060], p_{FDR}<0.001; $\beta_{ADHD\ PGS\text{-}TOT.A}$=0.027, 95%CI [0.011, 0.043], p_{FDR}=.001) (Appendix B, Supplementary Figure 2 and Supplementary Table 2).

These findings suggest that the association between the PGSs for ADHD, bipolar disorder and schizophrenia and individual symptoms of depression and anxiety may be driven mostly by the shared genetic liability between these disorders and depression. I nonetheless found significant

associations between ADHD and schizophrenia PGSs and individual symptoms even after accounting for the genetic propensity to depression in the ‘Multiple PGSs’ model.

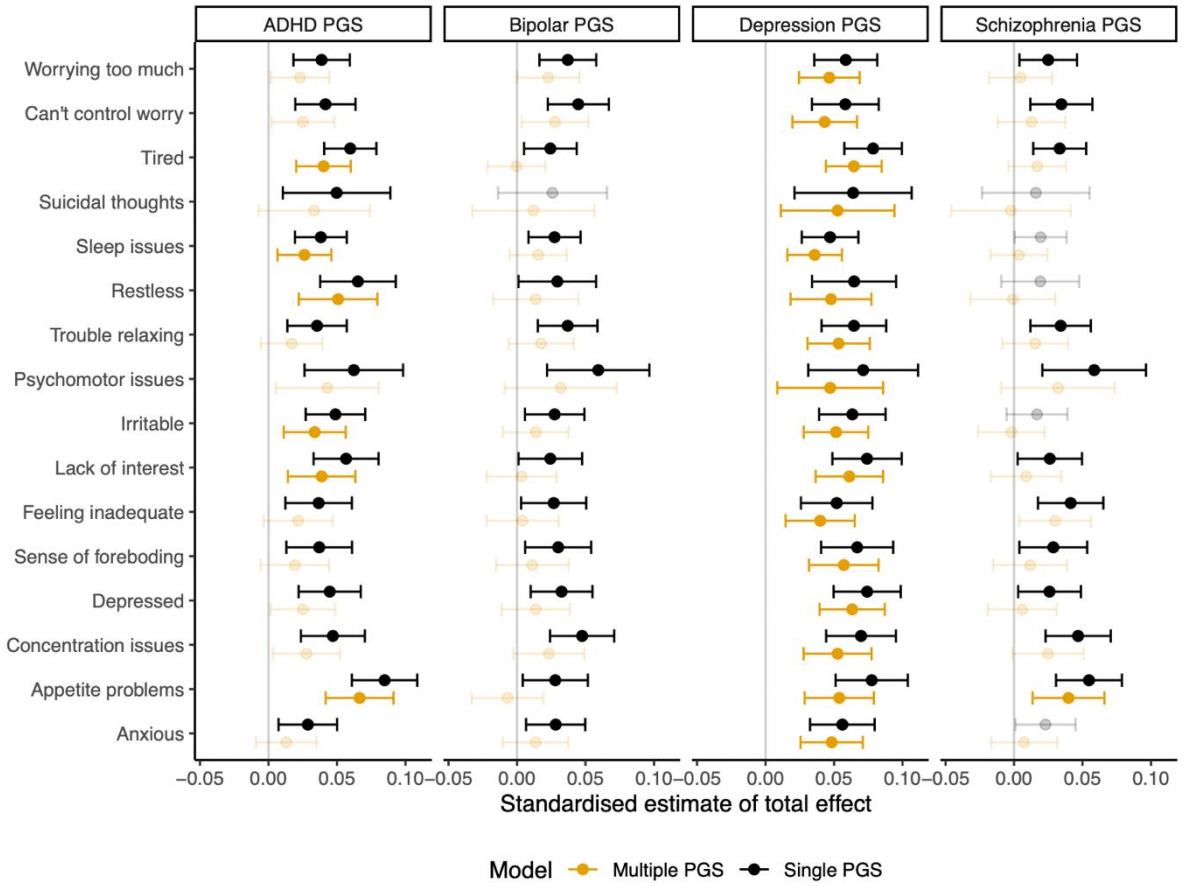


Figure 3.3: Total effects of polygenic scores on individual symptoms.

Standardised estimates of total effects in 'Multiple PGSs' model (yellow) and 'Single PGS' models (black) with 95% confidence intervals. Points are faded when estimates are non-significant based on FDR-corrected *p*-values. Estimates and CIs were pooled across 25 imputed datasets.

3.4.2 Associations between polygenic scores and brain mediators

In 'Single PGS' models, all PGSs, except the PGS for bipolar disorder, were significantly negatively associated with individual regional brain volumes (Appendix B, Supplementary Table 1). In particular, the depression PGS was negatively associated with mOFC, insula, cingulate and fusiform volumes, and the schizophrenia PGS was negatively associated with the mOFC and hippocampus volumes (**Figure 3.4**).

The depression PGS was not significantly associated with brain mediators in the 'Multiple PGSs' model (Appendix B, Supplementary Table 1). I found significant negative associations between all brain volumes and the ADHD PGS (ranging from the mOFC, $\beta_{\text{ADHD PGS-MOFC}}$=-0.050, 95%CI [-0.065, -0.034], p_{FDR}<0.001, to hippocampus, $\beta_{\text{ADHD PGS-HIP}}$=-0.031, 95%CI [-0.046, -0.016], p_{FDR}<0.001), a significant negative association between the schizophrenia PGS and the hippocampus ($\beta_{\text{SCZ PGS-HIP}}$=-0.021, 95%CI [-0.037, -0.005], p_{FDR}=0.047), as well as a positive association between the bipolar disorder PGS and the cingulate and insula ($\beta_{\text{BD PGS-CING}}$=0.023, 95%CI [0.006, 0.040], p_{FDR}=.043; $\beta_{\text{BD PGS-INS}}$=0.031, 95%CI [0.015, 0.047], p_{FDR}=.001).

This pattern of findings suggests that the associations between the polygenic risk for depression and regional brain volumes may be driven by the shared genetic liability with comorbid disorders, and in particular, neurodevelopmental conditions, such as ADHD.

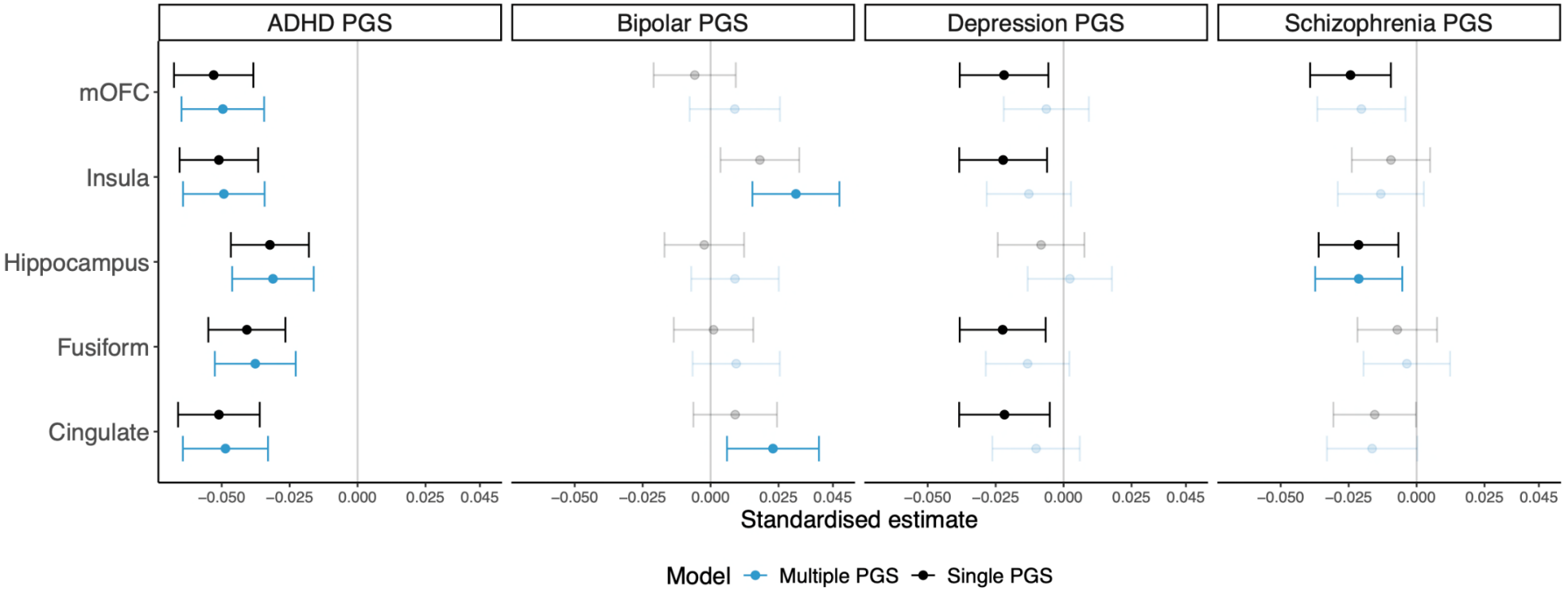


Figure 3.4: Associations between PGSs and brain mediators.

Standardised estimates of associations between PGSs and brain areas in 'Multiple PGSs' model (blue) and 'Single PGS' models (black) with 95% confidence intervals. Points are faded when estimates are non-significant based on FDR-corrected *p*-values. Estimates and CIs were pooled across 25 imputed datasets.

3.4.3 Associations between brain mediators and individual symptoms

I found small, significant, correlations between regional brain volumes and individual symptoms (ranging from insula and sleep problems, $r_{INS\text{-}SLE}$ =-0.069 95%CI [-0.085,-0.052], p_{FDR}<0.001, to hippocampus and irritability, $r_{HIP\text{-}IRR}$=0.031 95%CI [0.014, 0.047], p_{FDR}=.001) (Appendix B, Supplementary Table 3). In the 'Multiple PGSs' model, I found significant negative associations between tiredness, suicidal thoughts, sleep issues and lack of interest and individual brain areas (**Figure 3.5**) (ranging from $\beta_{HIP\text{-}SUI}$=-0.07 95%CI [-0.024,-0.116], p_{FDR}=.018, to $\beta_{CING\text{-}SLE}$=-0.027 95%CI [-0.047, -0.007], p_{FDR}=.047).

In contrast, I did not detect any significant associations between individual brain volumes and total depression and anxiety scores (Appendix B, Supplementary Figure 2 and Supplementary Table 2). These findings suggest that regional brain volumes are independently associated with a restricted number of depression and anxiety symptoms, and that focusing on summary scores can obscure these patterns of associations.

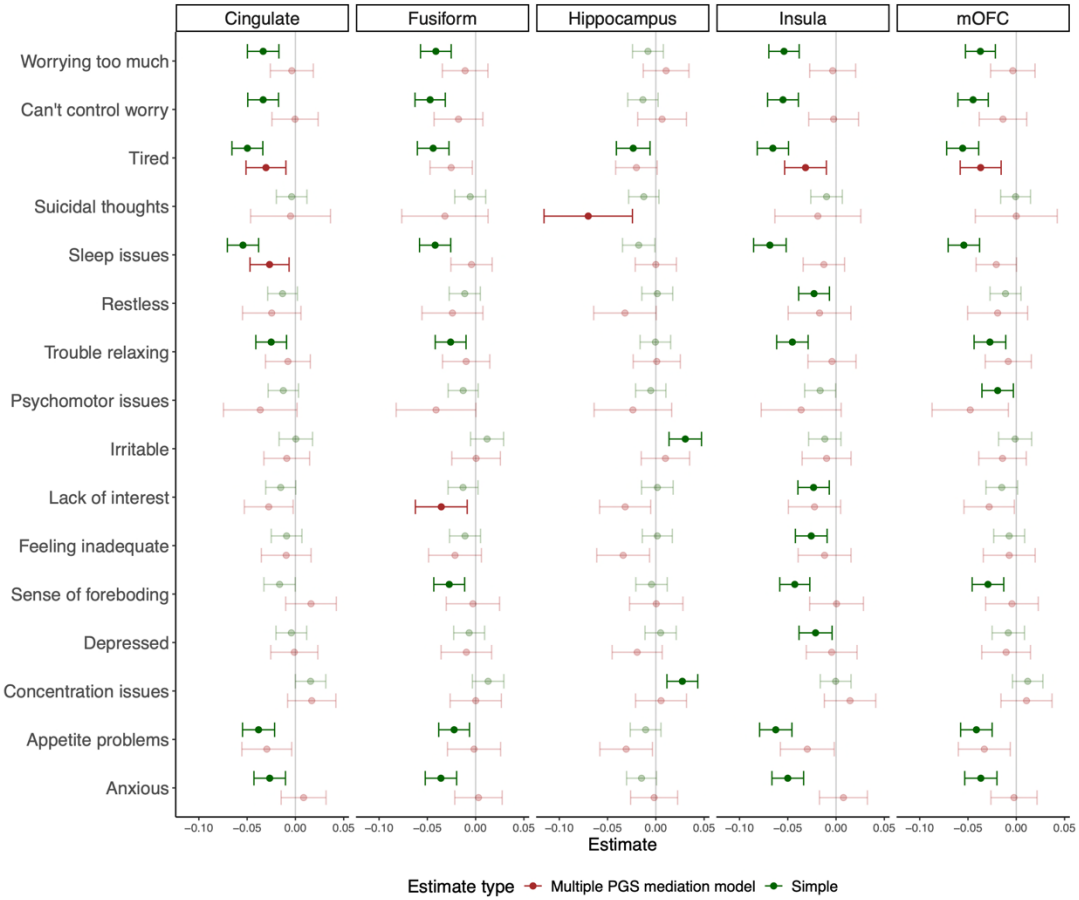


Figure 3.5: Associations between brain areas and individual symptoms.

Standardised estimates of associations between brain areas and symptoms in the 'Multiple PGSs' model (brown) and simple (green) correlations between brain areas and symptoms, with 95% confidence intervals. Points are faded when estimates are non-significant based on FDR-corrected *p*-values. Estimates and CIs were pooled across 25 imputed datasets.

3.4.4 Individual and total mediation effects

I did not find evidence for total or individual mediation effects in either the 'Multiple PGSs' or 'Total score' models. A significant total mediation effect of the association between tiredness and the ADHD PGS was found in the 'Single PGS' models (total mediated effect$_{\text{ADHD PGS-TIR}}$=0.007, 95%CI [0.003, 0.011], p_{FDR}=.011) (Appendix B, Supplementary Figure 1).

I observed small, non-significant differences between total and unmediated effects between PGSs and symptoms in the 'Multiple PGSs' model (Appendix B, Supplementary Figure 3). The largest differences (although non-significant) were between the total and unmediated effects of the PGS for ADHD and symptoms such as appetite, tiredness, restlessness, psychomotor issues, lack of interest and suicidal thoughts (differences total – unmediated > 0.004).

This pattern of non-significant results suggests that the associations between PGSs for depression, ADHD, bipolar disorder and schizophrenia, and individual symptoms of depression and anxiety may not be mediated by the volume of brain regions implicated in depression (and other disorders).

3.5 Discussion

In a large sample drawn from the UKB, I linked genetic, neuroimaging, and individual symptom measures, examining the mediating effects of brain structure on the associations between PGSs for psychiatric disorders and symptoms of depression and anxiety. I observed that PGSs for disorders that are comorbid with depression are associated with (i) individual symptoms of depression and anxiety (such as tiredness, restlessness, sleep and appetite problems) and (ii) regional brain volumes. Moreover, regional brain volumes are also associated with individual symptoms of depression and anxiety. Despite the associations between PGSs and brain volumes, and brain volumes and symptoms, the effects of PGSs on individual symptoms did not appear to be mediated by brain structure. Taken together, these findings suggest that aggregating symptoms may hide symptom-specific patterns of associations relevant to comorbidity in depression.

3.5.1 Associations between polygenic scores and individual symptoms

Symptom-level analyses showed novel patterns of associations between PGSs for psychiatric disorders and individual symptoms of depression and anxiety. First, I found that PGSs for disorders that are comorbid with depression, such as ADHD and schizophrenia, are associated with individual symptoms of depression and anxiety, even when adjusting for the effects of the PGS for depression. In particular, ADHD is associated with core depression symptoms, such as lack of interest in activities (i.e., anhedonia), and with a hyperactivity symptom common to both ADHD and depression (i.e.,

restlessness). Similarly, both the PGSs for schizophrenia and ADHD are associated with somatic symptoms of depression (i.e., tiredness, sleep and appetite problems). While I find similar associations when using total scores as outcomes, these findings suggest that the associations between the polygenic risk for disorders comorbid with depression and the depression phenotype may be driven by specific symptom subsets, which may include shared symptoms across disorders.

Second, I found that the PGS for depression is associated with all symptoms of depression and anxiety. Although these effects are attenuated when accounting for the effects of other PGSs, this result suggests that the depression PGS is associated with all features of depression, with comparable effect sizes. The depression cases in the GWAS used to derive the depression PGS were identified through structured diagnostic interviews,electronic health records, and self-report of a diagnosis or treatment by a medical professional (Wray et al., 2018). A subset of patients may have been assessed via widely used clinical diagnostic instruments (e.g., PHQ-9 and GAD-7) that mirror the mental health questionnaire included in the UKB and used in these analyses (Davis et al., 2020). Similar ways of assessing symptoms in base and target cohorts may have increased the prediction accuracy of PGSs.

3.5.2 Associations between polygenic scores and regional brain volumes

Moreover, I found associations between PGSs and volumes of individual brain areas associated with impairment in depression. First, I observed associations between PGSs for disorders comorbid with depression and individual brain

volumes when including all PGSs in the same model. In particular, the PGS for ADHD is negatively associated with all regional brain volumes in this study, including areas previously identified as being affected in ADHD across development, such as the hippocampus, fusiform gyrus and cingulate (Hoogman et al., 2017, 2019). Similarly, the schizophrenia PGS is associated with reduced volume in the hippocampus, a region reported to be impaired in schizophrenia (van Erp et al., 2016, 2018). Conversely, I identified a positive association between the PGS for bipolar disorder and volumes of the insula and cingulate, consistent with recent meta-analytic evidence of both increased and decreased white and grey brain matter volume in bipolar disorder, perhaps reflecting a pattern of generalised brain alterations (Angelescu et al., 2021).

Second, although I observed associations between the PGS for depression and individual brain areas, such as the mOFC, fusiform, cingulate and insula, these associations may be attributed to a shared genetic liability with ADHD, schizophrenia and bipolar disorder, indexed by PGSs in the 'Multiple PGSs' model. This pattern of results suggests that the genetic liability to disorders such as ADHD, schizophrenia, and bipolar disorder may drive the associations between the genetic risk for depression and alterations in brain regions associated with depression. Additionally, neural alterations observed in disorders comorbid with depression may be partially genetically influenced.

3.5.3 Recurrent associations with somatic symptoms of depression

Interestingly, some symptoms of depression and anxiety showed links across levels of organisation, associating with both genetic and neuroimaging measures. Specifically, somatic symptoms of depression, such as tiredness, sleep issues and appetite problems, showed independent associations with PGSs for mental health disorders and with individual brain areas. For example, tiredness was positively associated with the PGS for ADHD and depression, as well as with lower volumes in the cingulate, insula, and mOFC. The association between the ADHD PGS and tiredness also showed the largest (although non-significant) cumulative mediation effect of all brain areas. While tiredness and sleep problems were also more prevalent than other symptoms in the present UKB sample, they are among the most frequently repeated features across psychopathology diagnoses (Forbes et al., 2023).

These results identify somatic symptoms as non-specific indicators of psychopathology, which may have different aetiological factors compared to other symptoms of depression. Somatic symptoms may be influenced by genetic liability and neurobiological alterations to a greater extent than behavioural symptoms of depression. As suggested by Forbes et al. (2023), these symptoms may indicate a general response to psychological stress, common to mental and physical health disorders.

3.5.4 Implications of symptom-level analyses

Notably, by focusing on individual symptoms, I found previously unreported genetic and neuroimaging results, which may be obscured by aggregating symptoms. For example, I found an association between the ADHD PGS and total scores of depression and anxiety, which may be driven primarily by individual symptoms, such as restlessness, anhedonia, and somatic symptoms. Similarly, I did not find evidence of an association between total depression and anxiety scores and individual brain areas. However, zooming in on the symptom level, I found evidence of associations between brain area volumes and individual symptoms – for example, between fatigue and volumes of the cingulate, insula, and mOFC. These findings suggest that using total scores may fail to detect small, granular associations with individual symptoms. Although aggregate scores have clinical utility, they may hide important mechanistic information relevant to understanding the contributions of neural and genetic factors to mental health disorders and their comorbidity.

3.5.5 Absence of mediation effects

It is important to note that I did not find strong evidence for individual or total mediation effects of brain volumes on the association between PGSs and symptoms, as also reported in some recent studies (Alemany et al., 2019; Reus et al., 2017). There may be several reasons for this finding. First, the effect of PGSs may not be specific to the brain areas selected in this study, instead showing diffuse effects across the brain. Second, although I analysed a large sample for both neuroimaging and genetic analyses from the UKB, the effect size of a PGS is typically small, and it is worth noting that some

mediation effects were nominally significant before applying correction for multiple comparisons. Decomposing small effects to identify brain mediators may require larger samples. Lastly, although structural MRI measures appear to be more heritable than other imaging phenotypes (e.g., diffusion and functional MRI) (Elliott et al., 2018), widespread network-level dysfunctions are reported across mental health disorders (van den Heuvel & Sporns, 2019), suggesting that alternative brain markers, such as brain connectivity, may be better candidate mediators.

3.5.6 Limitations and conclusions

These findings should be considered in light of some limitations. First, the UKB is a population-based cohort, with low overall levels of symptoms of depression and anxiety. Future efforts should replicate these findings in cohorts enriched for clinical cases. Additionally, the UKB is affected by participation bias (Fry et al., 2017), an issue which may be exacerbated in the sample of participants who underwent MRI scanning (Lyall et al., 2022) and affects genetic analyses (Schoeler et al., 2023). Second, these analyses are limited to participants of European ancestry, and results should be replicated in more diverse samples as they become available for genetic analyses. Third, using individual symptoms, and, in particular, individual items on psychological scales as outcome measures, may increase measurement error and bias effect estimates.

To address the problem of missing data in the mental health questionnaire, I employed multiple imputation, which offers an effective strategy for handling missingness, particularly when data are Missing At

Random (MAR). This approach was selected for its flexibility and widespread application in psychopathology research (Woods et al., 2024). Multiple imputation retains partially observed cases, and recovers information on missing data by using auxiliary variables. This way, the potential bias that can arise when using listwise deletion is reduced. Statistical power is increased while preserving the uncertainty about missing values, with no new observations added to the dataset.

The auxiliary variables included in my multiple imputation strategy were genetic measures (PGS), mental health questionnaire data, brain data (IDPs), age and sex. Notably, potentially important auxiliary variables to be included (and available in UKB) include socioeconomic status and income, educational attainment, and previous psychopathology symptoms, as these factors are important predictors of mental health. An alternative approach includes inverse probability weighting (IPW), which adjusts for missing data by assigning greater weight to observed cases that are similar to those with missing data. For example, using IPW to correct for non-random participation in UKB can lead to less biased estimates in genetic analyses (Schoeler et al., 2023), although it may exacerbate bias arising from self-report inaccuracy (Schoeler et al., 2024).

In conclusion, I found evidence of symptom-specific patterns of genetic and neural associations in depression and anxiety in a large population-based sample drawn from the UKB. However, there was no clear evidence that the influence of genetic risk on symptoms of anxiety and depression was mediated by brain volumes. Symptom-level analyses may improve our understanding of

comorbidity, shared genetic architecture, and shared neural dysfunction across psychiatric disorders.

Chapter 4: The effect of sertraline on networks of mood and anxiety symptoms: secondary analysis of the PANDA randomised controlled trial

4.1 Abstract

Depression consists of heterogeneous symptoms that can occur in hundreds of possible combinations. However, intervention studies commonly operationalise depression as a homogenous condition. Here, I adopt a symptom-level approach to test the effects of the selective serotonin reuptake inhibitor (SSRI) sertraline on depression and anxiety symptoms, and their associations. Using data from the PANDA randomised controlled trial, I employ network models to estimate the effects of sertraline at different time-points (contemporaneous networks at 2, 6 and 12 weeks) and across time (temporally lagged networks). Results show that sertraline has beneficial effects on core depression and anxiety symptoms as early as after two weeks of treatment, counteracted by detrimental effects on somatic symptoms of depression. This intricate pattern of treatment effects is typically masked when measuring depression on a single dimension. Focusing on individual symptoms of depression and anxiety may shed light on the nature, effectiveness and timing of antidepressant action.

4.2 Introduction

Selective serotonin reuptake inhibitors (SSRIs) are a first-line treatment for depression and anxiety. Although meta-analytic evidence suggests they have modest effect sizes compared to placebo (Cipriani et al., 2018; Slee et al., 2019), SSRIs have been increasingly prescribed in recent years (NHS Digital, 2019). The response to antidepressants can take weeks to develop, and relatively little is known about the precise mechanism of action behind it (Otte et al., 2016; Rang et al., 2012).

Multiple lines of evidence indicate considerable heterogeneity in symptoms of depression and anxiety. For example, some symptoms of depression show larger associations with functional impairment and are differentially associated with environmental and genetic risk factors (Fried & Nesse, 2014; Piazza et al., 2024; Thorp et al., 2020). Similarly, studies focusing on individual symptoms have reported differential treatment responses to SSRIs across symptom subgroups. Commonly used SSRIs were found to be more effective at treating core emotional symptoms than somatic symptoms (Chekroud et al., 2017), suggesting that they may simultaneously be effective in alleviating a subset of symptoms while failing to treat or even exacerbating others.

Additionally, reciprocal causal associations between symptoms may lead to maladaptive cycles (Ebrahimi et al., 2024). For example, insomnia might cause concentration problems, which could, in turn, reduce self-esteem. Separating the direct and indirect effects of SSRIs on individual symptoms has

potentially important implications for understanding the mechanisms underlying interventions (Boschloo et al., 2023).

Network analysis is a useful framework that allows for the statistical modelling and visualisation of symptoms and their associations (Borsboom, 2017). In networks, symptoms are represented by nodes, while their associations are represented as edges between nodes (Epskamp, Borsboom, et al., 2018). In this framework, SSRIs could exert direct effects on individual symptoms, for example, by directly improving mood. In addition, network analysis can examine network structures, i.e., the presence or absence and magnitude of associations between symptoms. SSRIs could alter network structures (Borsboom, 2017), for example, by reducing the strength of the association between feelings of sadness and feelings of guilt.

Network studies have suggested that antidepressant treatment is associated with improvements in individual symptoms of depression and anxiety, such as feelings of guilt (Boschloo et al., 2023), anxiety and avoidance (Cervin et al., 2020; Zhou et al., 2022), depressed mood (Komulainen et al., 2021), and worry (Bekhuis et al., 2018). However, few such studies have included a placebo group (Cervin et al., 2020; Komulainen et al., 2021), which precludes drawing strong conclusions, and most have only compared pre- and post-treatment networks cross-sectionally (Bekhuis et al., 2018; Berlim et al., 2021; Bos et al., 2018; Boschloo et al., 2023; Madhoo & Levine, 2016), neglecting potentially important temporal associations between symptoms. New insights into the effects of sertraline can emerge from modelling temporal associations between symptoms in both treatment and placebo groups.

Therefore, this study tests the direct effects of SSRI treatment on symptoms of depression and anxiety, relative to placebo, both at a single time point and across time, and examines associations between these symptoms. Combining novel analytical approaches, I conduct a secondary analysis of a large placebo-controlled randomised trial on the effectiveness of sertraline for the treatment of depression (the PANDA trial) (Lewis et al., 2019). First, using a standard regression approach, I investigate the effects of sertraline on individual depression and anxiety symptoms, compared to placebo. Second, I investigate these effects while accounting for associations between symptoms with network analyses, at each time-point (contemporaneous networks) and across time (temporally lagged networks). Third, we compare the patterns of associations between symptoms (i.e., network structures, both contemporaneously and across time) between sertraline and placebo groups.

4.3 Methods

4.3.1 Sample and measures

The sample included patients from the PANDA trial (Appendix C, Supplementary Table 1) (Lewis et al., 2019). In this trial, 653 adult patients (384 female, mean age 39.7±14.96 years) with depressive symptoms were recruited in a primary care setting. Participants received either sertraline (50mg, once daily for one week, then 100mg daily for up to 11 weeks) (n=324, 203 female, mean age 39.7±14.6 years) or placebo (n=329, 181 female, 39.7±15.4 years), in a double-blind, randomised design. Details on recruitment, treatment allocation and randomisation are described in detail by Lewis et al., (2019) and Salaminios et al., (2017).

In the current analysis, I used the Patient Health Questionnaire (PHQ-9) (Kroenke et al., 2001), Beck Depression Inventory (BDI-II) (Beck et al., 1996) and Generalised Anxiety Disorder Assessment (GAD-7) (Spitzer et al., 2006) as measures of anxiety and depression symptoms, the physical health component of the Short Form Health Survey (SF-12) (Jenkinson et al., 1997), and a single item reflecting subjective improvement ("Compared to 2 weeks ago, how have your moods and feelings changed?" rated 1, 'I feel a lot better', to 5, 'I feel a lot worse'). Depression severity was assessed with total scores on the Clinical Interview Schedule—Revised (CIS-R) (Lewis et al., 1992), divided into three categories (0–11, 12–19, and ≥20). Patients were assessed at baseline and followed up at two weeks, six weeks, and twelve weeks post-baseline.

4.3.2 Statistical analysis

Analyses were carried out in R version 4.2.0 (R Core Team, 2022), and are outlined in **Figure 4.1**. All code used for the analyses is available on GitHub. Complete cases were used in each analysis step. High resolution plots and figures for this Chapter are available online.

4.3.2.1 Node selection

To reduce the number of network nodes, both for interpretability and to avoid collinearity issues, I examined items of the selected scales for content overlap, using a combination of data-driven analysis and conceptual inspection of item similarity. First, using the 'goldbricker' function in the R package *networktools* (version 1.5.0) (P. Jones, 2018), I identified correlated pairs of items that also showed a low proportion of statistically different correlations with other nodes (i.e., variable pairs with correlations $r \geq 0.5$ and less than 40% of significantly different correlations at alpha=5% were flagged, using the 'threshold' argument in the goldbricker function). Second, based on the data-driven information given by the goldbricker function, I inspected the identified, highly correlated pairs for content overlap and, when appropriate, decided to combine all items that had overlapping content by taking mean values (rounded to the next integer; see Appendix C Supplementary Table 2). For example, I combined BDI item 20 (tiredness of fatigue, from "I am no more tired or fatigued than usual" to "I am too tired or fatigued to do most of the things I used to do"), BDI item 15 (loss of energy, from "I have as much energy as ever" to "I don't have enough energy to do anything") and PHQ item 4 ("Feeling tired or having little energy"), taking the mean of the three items and

creating a single ‘Tiredness’ variable. The selection procedure resulted in 21 symptoms.

4.3.2.2 Change in symptoms over time

I used standard linear mixed regression models to analyse the effects of time, treatment, and their interaction on the 21 symptoms derived by node selection, using the R package *lmerTest* (version 3.1.3), restricted maximum likelihood estimation and Satterthwaite’s method for approximating degrees of freedom (Kuznetsova et al., 2017). These models included time (two, six and twelve weeks) and individuals as random effects, allowing for random slopes. Site, the corresponding baseline symptom score, depression duration, and treatment allocation were included as fixed effects, with an interaction between treatment and time. Effect sizes (η^2, i.e., the amount of variation in each item explained by predictors) and associated 95% confidence intervals were obtained using the R package *effectsize* (version 0.7.0) (Ben-Shachar et al., 2020). *P*-values were adjusted for multiple comparisons (21 tests) with False Discovery Rate correction (FDR) using the Benjamini-Hochberg method (alpha=5%) and the R package *stats* (version 4.2.0) (R Core Team, 2022).

4.3.2.3 Network analyses

To compare the present analyses with prior studies, I separately modelled each time-point at which symptoms were measured (“Contemporaneous” networks) (**Figure 4.1**)**.** I then included associations between symptoms across time (“Temporally lagged” networks). Within both network types, I modelled treatment allocation as a network node to estimate the direct effect of sertraline on individual symptoms while accounting for all other associations

in a network. For example, I estimated the association between the treatment node and feelings of sadness, while accounting for all associations between symptoms. I then focused on a comparison of network structures between sertraline and placebo groups ("Network structure comparisons") in both contemporaneous and temporally lagged networks. This allowed me to establish whether individuals in either group had a greater number of non-zero associations between symptoms or showed stronger associations between symptoms. For example, I estimated whether there was a weaker association between feelings of sadness and low self-esteem in the sertraline group, relative to the placebo group, at the two-week time-point.

All item-level data used in networks was adjusted for covariates and baseline variables associated with missingness (identified in the main PANDA trial results) using linear regression models. In these models, each item was predicted by sex, age, surgery site, baseline item values, depression severity (CIS-R) and duration, ethnicity ('White' or 'Ethnic minority'), financial difficulty ('Comfortably/Alright', 'Just about coping' or 'Finding it difficult'), previous antidepressant use ('Yes' or 'No'), marital status ('Married/Living as married', 'Single' or 'Separated, divorced or widowed') and significant life events (number of life events in the past six months). Standardised residuals obtained from linear regressions were then used in network analyses.

4.3.2.4 Contemporaneous networks

I estimated one network per time-point using the *mgm* R package (version 1.2.13) (Haslbeck & Waldorp, 2020), modelling the selected symptoms and a node indicating treatment allocation (0=placebo, 1=sertraline) (Blanken et al.,

2019). The Least Absolute Shrinkage Selection Operator (LASSO) was used to minimise the number of spurious edges, and cross-validation was used to select the LASSO tuning parameter. In the resulting networks, edges represent partial correlations (*r*), and nodes represent symptoms at each time-point.

4.3.2.5 Network structure comparison in contemporaneous networks

I tested the null hypothesis that network edges were equal across sertraline and placebo groups for each contemporaneous network with a resampling-based permutation test (Network Comparison Test, NCT, with 100 iterations) (van Borkulo, 2018).

4.3.2.6 Temporally lagged networks

I estimated a cross-lagged panel model including all symptoms (as observed variables) with the R package *lavaan* (version 0.6.12) (Rosseel, 2012) using full information maximum likelihood estimation, including treatment allocation as a predictor (Appendix C, Supplementary Figure 1) (Mulder & Hamaker, 2021). In this model, each symptom at one time-point was regressed on all symptoms at the previous time-point, allowing me to model the association of one symptom with another later symptom (cross-lagged paths) and with itself over time (autoregressive paths), while controlling for the associations with all other symptoms at the previous time-point (Wysocki et al., 2022). For example, I modelled the effect of concentration problems at the two-week time-point on sleep problems at the six-week time-point, while controlling for associations with all other symptoms at the two-week time-point.

The resulting standardised regression coefficients (β) were visualised as a network of directed edges.

4.3.2.7 Network structure comparison in temporally lagged networks

I compared groups by testing whether all edges between network nodes had comparable weights in the sertraline and placebo groups. I constructed a cross-lagged panel model without including treatment allocation as a variable (Appendix C, Supplementary Figure 2). I then compared a model where all regression coefficients were set to be equal between groups (Model 1) to a model where all coefficients were allowed to freely vary between groups (Model 2) using common fit indices (Akaike Information Criterion, AIC; Bayesian Information Criterion, BIC).

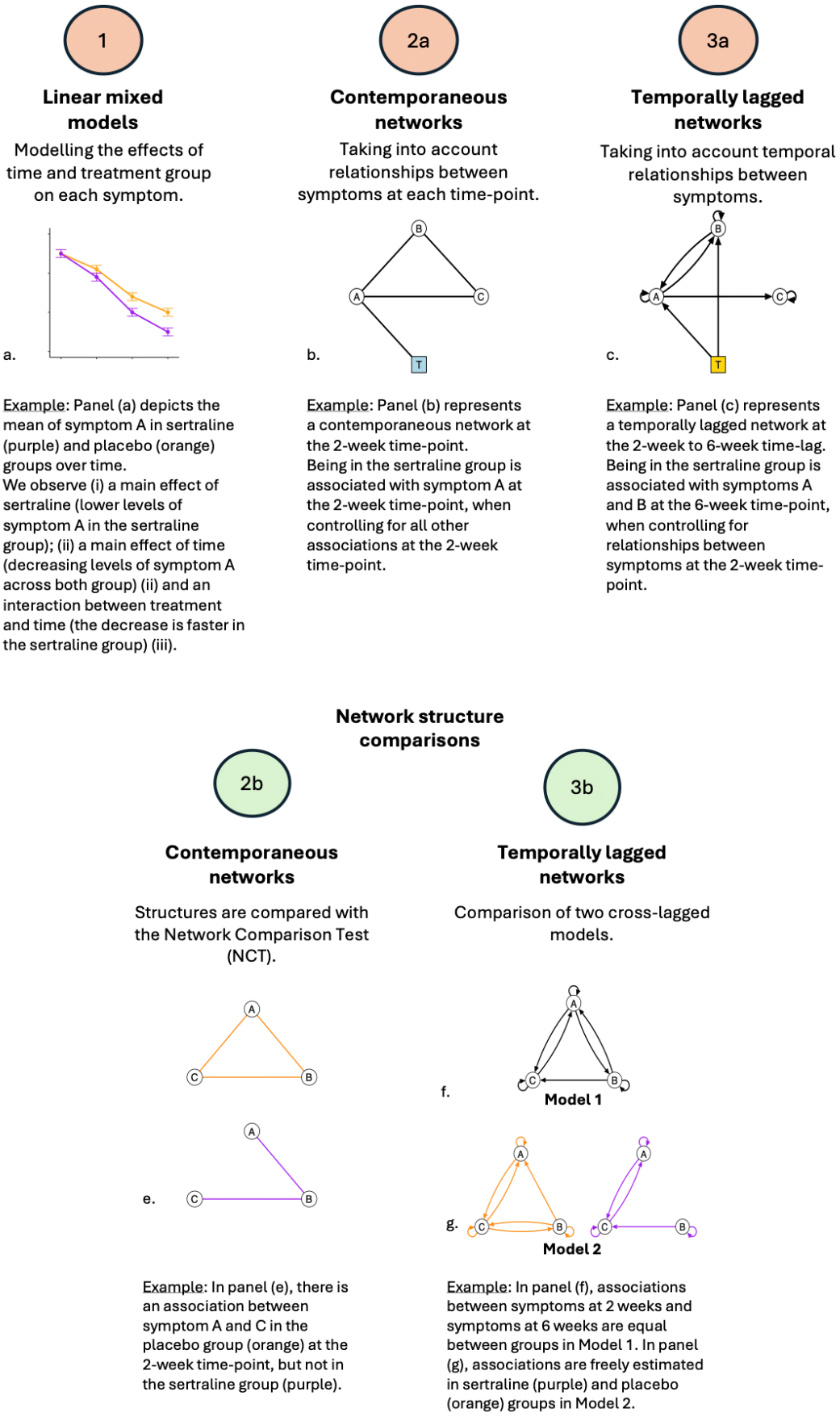


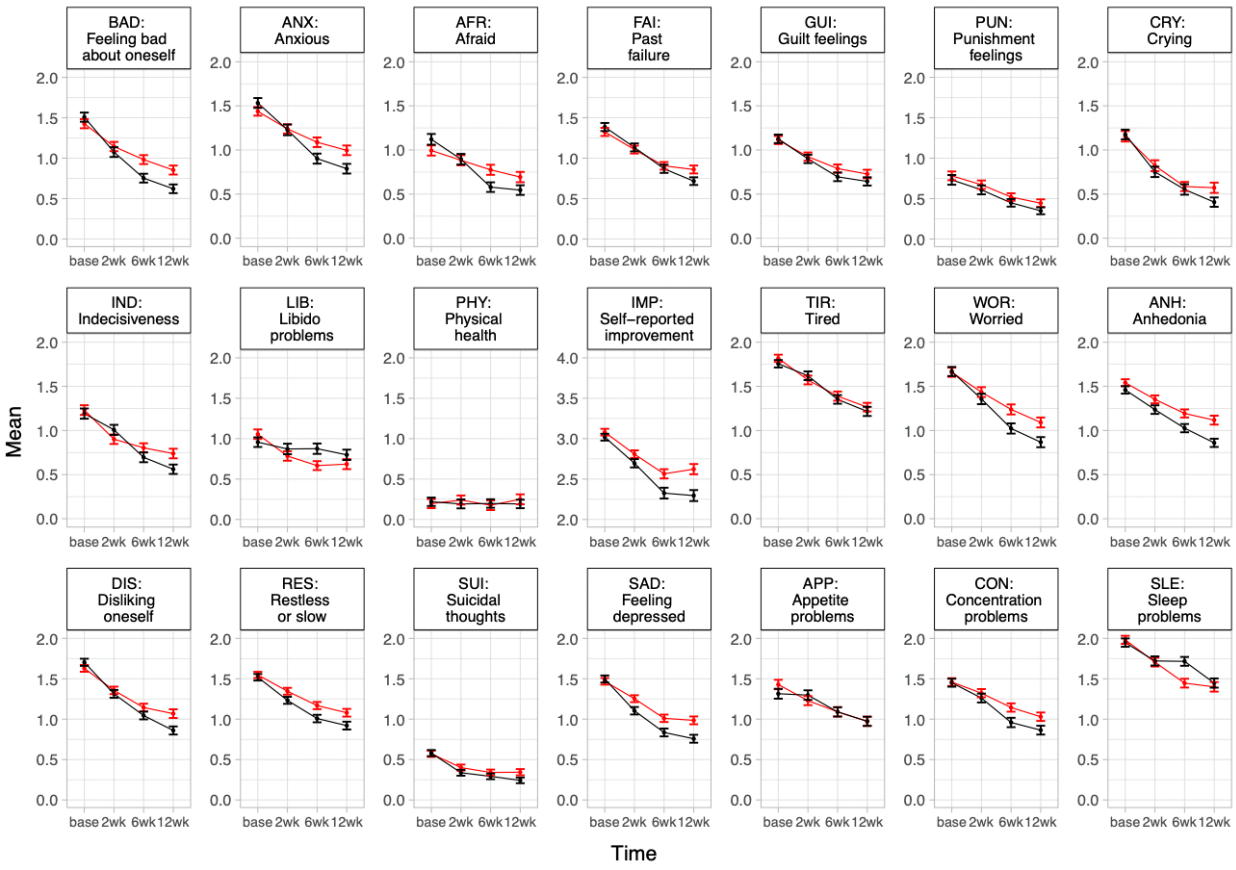
Figure 4.1: Symptom-level analyses included in Chapter 4 (further discussed in Methods)

4.4 Results

4.4.1 Effect of sertraline on individual symptoms

A maximum sample of n=571 individuals with complete cases for each symptom was included in this analysis (Appendix C, Supplementary Table 3). Mixed models indicated significant main effects of sertraline on all symptoms (accounting for baseline score), with small effect sizes (η^2=0.007-0.019) (**Figure 4.2**), except for problems with appetite (APP), crying (CRY), feelings of guilt (GUI), physical health (PHY), feelings of self-punishment (PUN), sleep (SLE) and tiredness (TIR). The largest beneficial effects of sertraline were on feelings of self-loathing (DIS), p_{FDR}<0.001, η^2=0.019, 95% CI [0.006, 0.038], feeling bad about oneself (BAD), p_{FDR} <0.001, η^2=0.018, 95% CI [0.006, 0.037], and anhedonia (ANH), p_{FDR} <0.001, η^2=0.017, 95% CI [0.005, 0.035]. There were significant main effects of time on all symptoms except problems with libido (LIB), physical health, and suicidal thoughts (SUI) (Appendix C, Supplementary Table 4). Following corrections for multiple comparisons, no treatment-by-time interactions achieved significance (Appendix C, Supplementary Table 4).

a.


BAD: Feeling bad about oneself
ANX: Anxious
AFR: Afraid
FAI: Past failure
GUI: Guilt feelings
PUN: Punishment feelings
CRY: Crying
IND: Indecisiveness
LIB: Libido problems
PHY: Physical health
IMP: Self−reported improvement
TIR: Tired
WOR: Worried
ANH: Anhedonia
DIS: Disliking oneself
RES: Restless or slow
SUI: Suicidal thoughts
SAD: Feeling depressed
APP: Appetite problems
CON: Concentration problems
SLE: Sleep problems
Mean
base 2wk 6wk 12wk
Time
Group Placebo Sertraline

b.

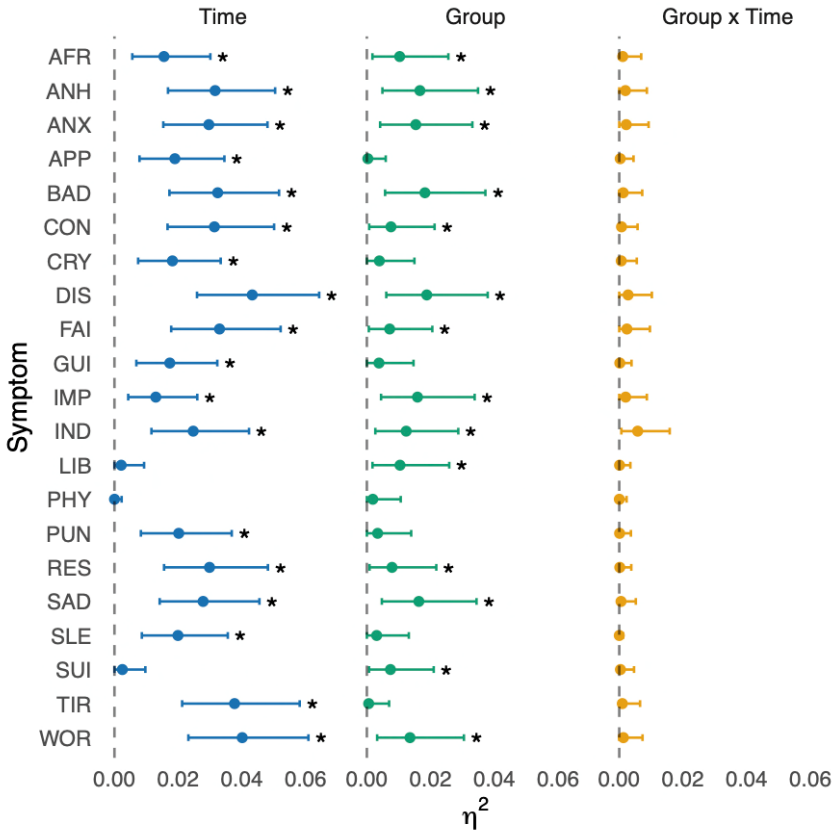

Time
Group
Group x Time
Symptom
AFR
ANH
ANX
APP
BAD
CON
CRY
DIS
FAI
GUI
IMP
IND
LIB
PHY
PUN
RES
SAD
SLE
SUI
TIR
WOR
0.00 0.02 0.04 0.06
η2

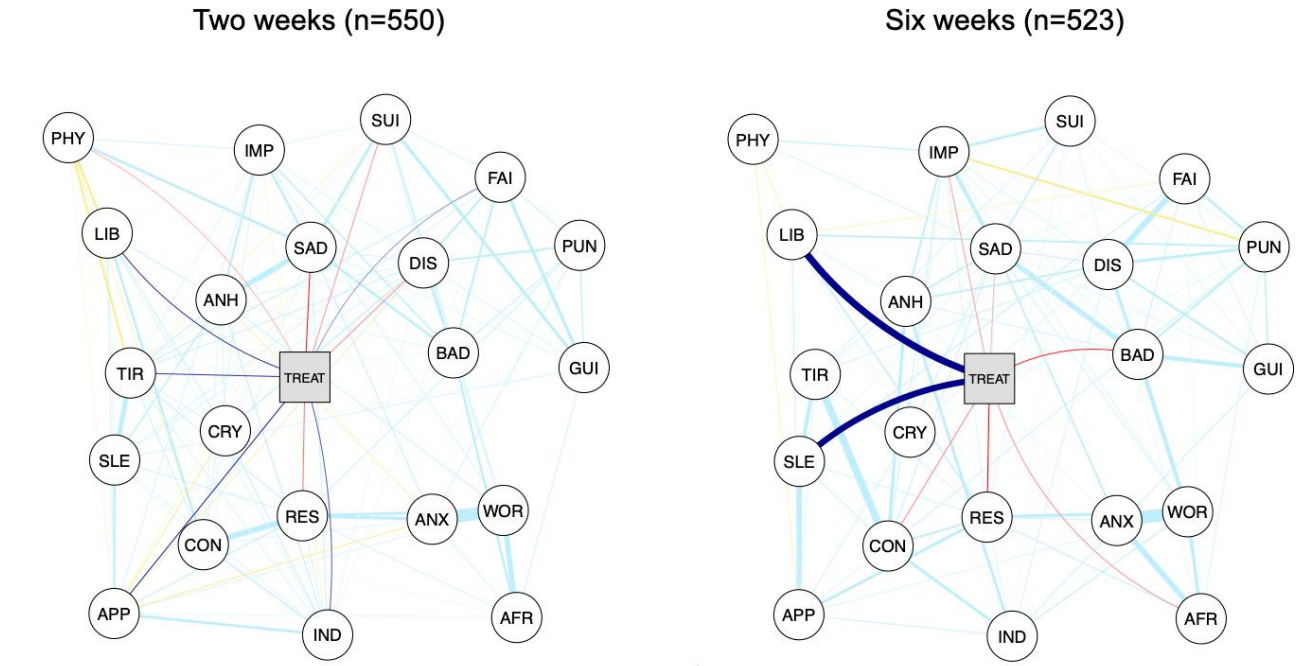
Figure 4.2 (a-b): Effects of treatment and time on mean symptoms.
(a) Means (± standard errors) of symptoms of depression and anxiety (derived in the node selection step) at baseline, 2 weeks, 6 weeks and 12 weeks; **(b)** effect sizes (η^2) of time, treatment group and group by time interactions and associated confidence intervals (95% CI) in linear mixed models for each symptom. In these models, baseline scores for each symptom were included as fixed effects. Asterisks indicate a significant effect (based on FDR-corrected *p*-values).

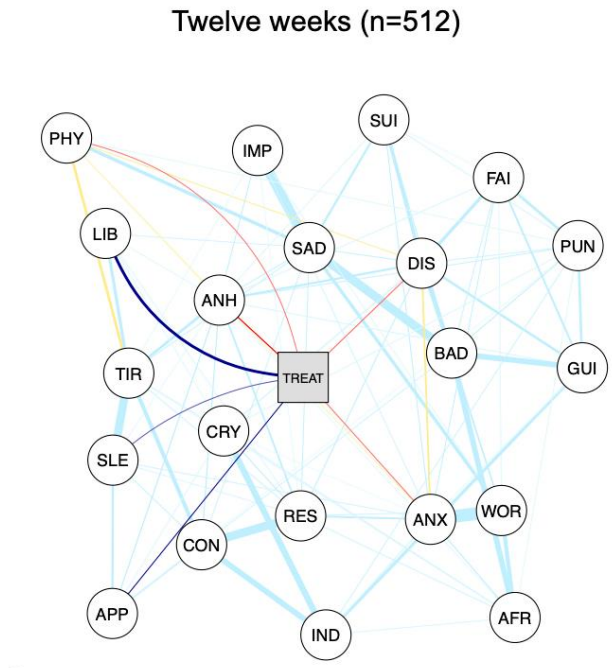
4.4.2 Contemporaneous networks

I found beneficial effects of sertraline on symptoms across all assessments (n_{2weeks}=550, n_{6weeks}=523, $n_{12weeks}$=512) in contemporaneous networks (**Figure 4.3**; Appendix C, Supplementary Tables 5-7). Sertraline treatment caused lower feelings of sadness (SAD, r_{2weeks}=-0.092), restlessness (RES, r_{2weeks}=-0.053), self-loathing (r_{2weeks}=-0.044), suicidal thoughts (r_{2weeks}=-0.039) and physical health problems (r_{2weeks}=-0.028) at the two-week time-point, lower levels of feeling bad about oneself (r_{6weeks}=-0.087), sadness (r_{2weeks}=-0.027), and feeling afraid (AFR, r_{6weeks}=-0.041), restlessness (r_{6weeks}= -0.098) and concentration problems (CON, r_{6weeks}=-0.0046) at the six-week time-point, and lower levels of anxiety (ANX, $r_{12weeks}$=-0.057), physical health problems ($r_{12weeks}$=-0.055), anhedonia ($r_{12weeks}$=-0.103) and self-loathing ($r_{12weeks}$=-0.061) at the twelve-week time-point. In addition, sertraline treatment caused higher self-reported improvement (IMP) at six weeks (r_{6weeks}=-0.036). However, sertraline also had detrimental effects at all time-points, such as on problems with sleep (r_{6weeks}=0.219, $r_{12weeks}$=0.065), appetite (r_{2weeks}=0.089, $r_{12weeks}$=0.099) and libido (r_{2weeks}=0.082, r_{6weeks}=0.235, $r_{12weeks}$=0.132), tiredness (r_{2weeks}=0.077), fatigue (FAI, r_{2weeks}=0.039), and indecisiveness (IND, r_{2weeks}=0.065).

4.4.3 Network structure comparison in contemporaneous networks

The Network Comparison Test revealed no significant differences in network structure between placebo and sertraline networks (all p>0.05).





AFR	Feeling afraid
ANH	Loss of interest and pleasure in everyday life
ANX	Feeling nervous or anxious
APP	Lack of appetite or eating too much
BAD	Feeling bad about oneself
CON	Concentration problems
CRY	Crying
DIS	Disliking oneself
FAI	Past failure
GUI	Guilty feelings
IMP	Self-reported improvement
IND	Indecisiveness
LIB	Loss of interest in sex
PHY	General physical health
PUN	Punishment feelings
RES	Being restless or slow
SAD	Feeling sad or depressed
SLE	Sleep problems
SUI	Suicidal thoughts
TIR	Feeling tired
WOR	Feeling worried
TREAT	Treatment allocation

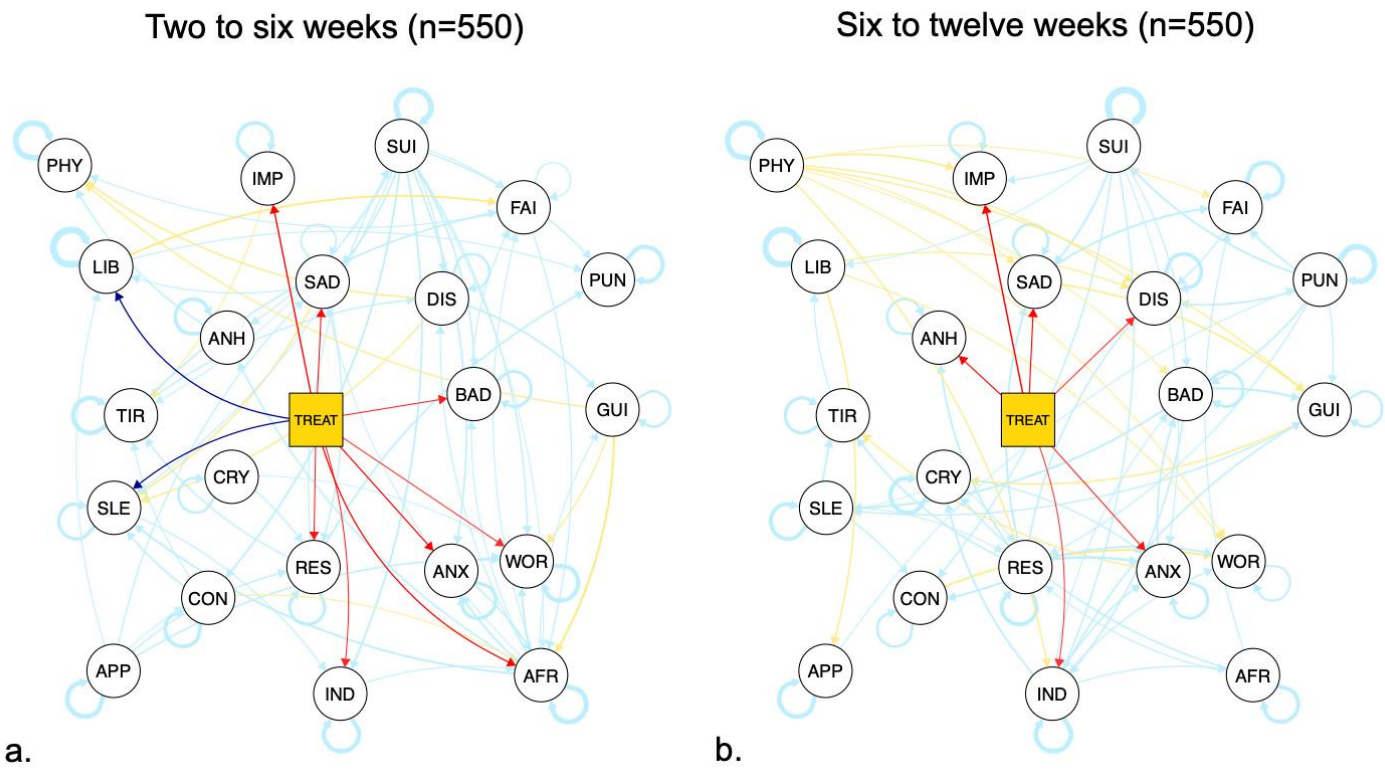
Figure 4.3 (a-c): Contemporaneous networks of symptoms of depression and anxiety. In all networks, thicker edges indicate larger associations. To highlight connections to the treatment node, positive associations (detrimental effects) with the treatment node (centre) are in dark blue and negative associations (beneficial effects) in red. Positive associations between symptoms are in light blue and negative associations in yellow. Networks were plotted with an identical layout to better compare results.

4.4.4 Temporally lagged networks

Sertraline caused lower symptoms of depression compared to placebo at all time points (n=550) when controlling for temporal associations at previous time-points (**Figure 4.4** and Appendix C, Supplementary Tables 8-9). For example, when accounting for symptoms at two weeks, sertraline caused, at six weeks, a reduction in feeling sad (β_{6weeks}=-0.096), bad about oneself (β_{6weeks} =-0.090) and afraid (β_{6weeks}=-0.114), restlessness (β_{6weeks}=-0.091), anxiety (β_{6weeks}=-0.110), worry (WOR, β_{6weeks}=-0.083), and indecisiveness (β_{6weeks}=-0.086). Moreover, even when accounting for symptoms at six weeks, sertraline still caused, at twelve weeks, a reduction in feeling sad ($\beta_{12weeks}$=-0.106), anxiety ($\beta_{12weeks}$=-0.092), anhedonia ($\beta 1_{2weeks}$=-0.105), self-loathing ($\beta_{12weeks}$=-0.084) and indecisiveness ($\beta_{12weeks}$=-0.081). Notably, sertraline treatment consistently caused self-reported improvement over time (β_{6weeks}=-0.121, $\beta_{12weeks}$=-0.130), but also caused problems with libido (β_{6weeks}=0.116) and sleep (β_{6weeks}=0.113) during the middle of treatment.

4.4.5 Network structure comparison in temporally lagged networks

I found no significant structural network differences between sertraline and placebo groups. The cross-lagged model where edges were set to be equal across groups (Model 1) had better support than the model where edges were free to vary across groups (Model 2) (BIC_{Model1}= 58,678, BIC_{Model2}= 63,257, AIC_{Model1}= 52,343, AIC_{Model2}= 53,120; Appendix C, Supplementary Table 10).



AFR	Feeling afraid	DIS	Disliking oneself	RES	Being restless or slow
ANH	Loss of interest and pleasure	FAI	Past failure	SAD	Feeling sad or depressed
ANX	Feeling nervous or anxious	GUI	Guilty feelings	SLE	Sleep problems
APP	Lack of appetite or eating too much	IMP	Self-reported improvement	SUI	Suicidal thoughts
BAD	Feeling bad about oneself	IND	Indecisiveness	TIR	Feeling tired
CON	Concentration problems	LIB	Loss of interest in sex	WOR	Feeling worried
CRY	Crying	PHY	General physical health	TREAT	Treatment allocation
		PUN	Punishment feelings		

Figure 4.4 (a-b): Temporally lagged networks of symptoms of depression and anxiety. Thicker edges indicate larger associations. Directed arrows represent cross-lagged associations and looped arrows represent autoregressive associations. To highlight connections to the treatment node, positive associations (detrimental effects) with the treatment node (centre) are in dark blue and negative associations (beneficial effects) in red. Positive associations between symptoms are in light blue and negative associations in yellow. Networks were plotted with an identical layout to better compare results.

4.5 Discussion

This study examined the effects of sertraline on symptoms of anxiety and depression and their associations in a sample drawn from a large placebo-controlled randomised trial. First, I found beneficial effects of sertraline on most symptoms of depression and anxiety when using typical analytical approaches (linear mixed models). Second, by accounting for associations between symptoms in network analyses, I found early effects on core emotional and volitional symptoms of depression and all symptoms of anxiety at around two weeks of treatment. These early beneficial effects may be masked when outcomes are measured using a single summary score by concurrent detrimental effects on somatic symptoms, which were also clear at two weeks. Finally, I found no evidence of differences in patterns of associations between symptoms (network structures), either at each time-point or across time, between treatment groups.

Adjusting for associations between symptoms showed that antidepressants may act more rapidly on some symptoms of depression than has previously been suggested using a single summary score of symptoms (Rang et al., 2012). When accounting for associations at each time-point (contemporaneous networks), I found a rapid, albeit small, effect of sertraline on sad mood compared to placebo, appearing around two weeks. In addition, analyses that account for temporal associations (temporally lagged networks) suggested that sertraline caused a reduction in all included anxiety symptoms, which is consistent with the (sum-score) results of the PANDA trial. However, importantly, using temporally lagged networks, I find an additional clear

reduction in core symptoms of depression, such as feeling sad and bad about oneself, as early as six weeks. While these network findings are partially mirrored by typical analyses that do not account for associations between symptoms, the network results suggest that sertraline may have an early effect on core symptoms of depression (such as sadness).

Importantly, these findings point to a pattern of contrasting effects of sertraline, with both beneficial and detrimental effects compared to placebo. Although the main results of the PANDA trial indicated no differences in adverse effects between groups, somatic symptoms of depression included in the present analyses are also frequently reported side effects of SSRIs (Rang et al., 2012). While I did not observe detrimental effects on sleep, tiredness and appetite when only examining symptoms individually (in linear mixed models), taking into consideration associations between symptoms provided additional sensitivity, revealing some detrimental effects of sertraline on libido, tiredness and appetite as early at two weeks, and on sleep and libido at six weeks. However, I did not detect additional effects at twelve weeks of treatment, beyond those at six weeks. In contrast, I found a continued beneficial effect of sertraline on depression and anxiety symptoms beyond six weeks of treatment, independent of its prior effects. Therefore, the adverse impact on somatic symptoms may peak and stabilise within six weeks of continued sertraline administration, and it may be counteracted by improvements in other symptoms.

This pattern of opposing effects on symptoms would be overlooked in analyses using summary scores on depression scales (e.g., BDI-II and PHQ-

9) as primary outcomes. On the contrary, summary scores on anxiety scales (e.g., GAD-7) may be more sensitive to certain improvements, as they may not include somatic symptoms associated with medication. Therefore, it is possible that the effects on depression reported in the primary analyses of the PANDA trial were partially attenuated by the inclusion of physiological indicators in main outcome measures (e.g., sleep and appetite items in the PHQ-9).

Finally, although I found direct effects of active treatment, I did not find evidence of different patterns of associations between symptoms across treatment groups (i.e., differences in network structures). This suggests that antidepressant treatment may not alter the associations between symptoms. In other words, although sertraline may cause an improvement in core symptoms, it may not change their reciprocal associations. For example, sertraline may, on average, improve sad mood and worry, but it may not alter the extent to which these two symptoms are associated with each other. Therefore, sertraline does not seem to operate via interrupting maladaptive reinforcements cycles between symptoms.

The interpretation of these findings has some limitations. First, psychological networks are dependent on the choice of network nodes (Borsboom et al., 2021; Borsboom & Cramer, 2013; Epskamp & Fried, 2018). Therefore, these findings are conditional on the selection of symptoms from commonly used depression and anxiety scales. However, the PHQ-9 and GAD-7 include all the common symptoms of both depression and anxiety. Second, these findings should be further confirmed and replicated in

independent samples. Third, some symptoms of depression and anxiety may be measured more reliably than others, and are therefore more likely to be detected in network edges. Lastly, the cross-lagged panel model used in this study does not account for stable, trait-like individual differences (Hamaker et al., 2015). While autoregressive paths in a cross-lagged panel model can account for temporal stability (the degree to which people maintain their rank order over time), this approach does not distinguish between- and within-person dynamics. As a result, stable traits may be misinterpreted as time-varying effects, potentially biasing estimates of cross-lagged paths (e.g., the effect of a symptom at one time point on a symptom at a subsequent time point). In contrast, the random intercept cross-lagged panel model (RI-CLPM) explicitly separates these levels by including a random intercept to capture time-invariant, trait-like factors (Mulder & Hamaker, 2021), allowing for a more accurate estimation of within-person dynamics and causal effects.

In conclusion, this study shows that sertraline has direct effects on individual anxiety and depression symptoms, as early as around two weeks of treatment, although it does not change associations between symptoms. Although the PANDA study found no evidence for an effect on depression at six weeks after starting sertraline, I observed effects of sertraline on depression symptoms as early as two weeks. These beneficial effects may have been masked by detrimental effects on somatic symptoms such as libido and sleep. Using a network approach can reveal novel insights into the effectiveness, the timing, and the direct pathways of antidepressant action by taking into consideration individual symptoms and their associations.

Chapter 5: General Discussion

This thesis presents three studies that take a symptom-level approach to psychopathology to better understand symptom heterogeneity in depression and comorbid disorders. This chapter summarises the main findings of each study, interprets key results, examines implications for future research, and considers their relevance for clinical translation.

5.1 Summary of findings

The findings of this thesis indicate that aggregating heterogeneous symptoms of depression into summary scores may obscure critical information about genetic risk, neurobiological mechanisms, and treatment response. Measuring depression along a single dimension fails to fully capture the disorder. In contrast, analysing its individual symptoms provides a more nuanced description that aligns more closely with patterns of comorbidity.

Chapter 2 examined the link between genetic risk and individual indicators of childhood psychopathology. Using cross-sectional network analysis and PGSs for depression and related traits, I analysed data from a primary sample drawn from ALSPAC and replicated findings in an independent sample drawn from TEDS. The results showed that PGSs were directly linked with restricted subsets of indicators. Specifically, psychiatric PGSs were associated with both cross-trait and trait-relevant symptoms, while non-psychiatric PGSs were associated with a broad range of emotional and behavioural difficulties.

Chapter 3 expanded on the findings of Chapter 2 by exploring links between the genetic risk for depression and comorbid disorders, brain morphology, and individual symptoms. Specifically, I investigated whether regional brain volumes mediate the relationship between PGSs and individual symptoms of depression and anxiety in the UK Biobank. The results indicated that PGSs for disorders comorbid with depression were associated with specific symptoms of depression and anxiety. Similarly, regional brain volumes were associated with individual symptoms, revealing symptom-specific patterns that are obscured when depression is measured with summary scores. However, surprisingly, regional brain volumes did not mediate the relationship between PGSs and symptoms.

Chapter 4 examined the effects of the SSRI sertraline on individual symptoms of depression and anxiety, as well as their reciprocal cross-sectional and longitudinal associations, using data from the PANDA RCT. The results showed that sertraline had beneficial effects on core symptoms of depression and anxiety, emerging after about two weeks of treatment – earlier than previously reported. However, these beneficial effects were counteracted by detrimental effects on somatic symptoms. Additionally, sertraline did not alter associations between symptoms (i.e., network structures). This complex pattern of opposing effects would be obscured when using summary scores as outcomes.

In the following section, I discuss cross-chapter themes, focusing on the insights derived from symptom-level approaches on research into comorbidity (Section 5.2) and recurrent patterns of associations with somatic symptoms of

depression (Section 5.3). Finally, I examine the relevance of findings to psychiatric nosology (Section 5.4), general limitations (Section 5.6), and the implications of this thesis for research and clinical practice (Section 5.7).

5.2 Comorbidity in depression: insights from a symptom-based approach

5.2.1 Beyond aggregate measures: symptom-specific associations with brain structure and treatment response

In Chapter 3, I found that the volumes of brain areas previously implicated in both depression and comorbid disorders were associated with individual symptoms of depression and anxiety. For example, cingulate volume was linked to tiredness and sleep, while fusiform gyrus volume was associated with anhedonia. In contrast, total depression and anxiety scores showed no significant associations with regional brain volumes. These findings suggest that efforts to identify reliable biomarkers may be hindered by suboptimal outcome measures – specifically, treating depression as a unitary construct may hide potentially critical information on comorbidity. Indeed, comorbidity may stem from shared neurobiological mechanisms affecting common symptoms (e.g., somatic symptoms, Section 5.3), rather than individual disorders. A symptom-level approach may therefore provide a clearer understanding of the neurobiological basis of depression and its comorbidities than total disorder scores.

Chapter 4 builds on this evidence, showing that sertraline had both beneficial and detrimental effects on individual symptoms of depression and anxiety (compared to placebo), which may act in opposition, and emerged as

early as two weeks into treatment. Notably, the primary results of the PANDA trial, which relied on sum-scores, found no evidence of early effects on depression, and only weak evidence of effects after twelve weeks of treatment (Lewis et al., 2019). By focusing on individual symptoms, I detected small but significant early effects on core symptoms of depression, suggesting that the primary PANDA trial findings may have partially been attenuated by the use of sum-scores as main outcome measure.

This complex pattern of symptom-specific effects may help explain why the response to antidepressants can take several weeks to develop, as suggested in the literature (Walsh & Harmer, 2015). For example, sertraline may simultaneously improve mood and negatively impact sleep and appetite. Although the study I conducted in Chapter 4 did not directly investigate underlying biological mechanisms, symptom-specific effects could clarify why SSRIs like sertraline are effective across multiple conditions (Bacaltchuk & Hay, 2003; Soomro et al., 2008; van der Linden et al., 2000). Rather than targeting a single disorder, SSRIs may influence shared symptom pathways (e.g., mood, sleep, fatigue) that cut across diagnostic categories. Symptom-level approaches can reveal these transdiagnostic effects and thus inform the development of treatments that target common symptom mechanisms underlying comorbid conditions.

5.2.2 Cross-trait associations between genetic risk and individual symptoms

The symptom-level analyses in this thesis have uncovered important associations between genetic risk and individual symptoms relevant to comorbidity.

Chapters 2 and 3 showed that PGSs for mental health disorders are associated with indicators beyond those typically linked to their corresponding traits. For example, in Chapter 2, the anxiety PGS was associated with loneliness in a sample of children. Non-psychiatric PGSs, such as those for BMI and educational attainment, were associated with a variety of emotional and behavioural problems in childhood. In Chapter 3, the ADHD PGS was found to be associated with anhedonia, a core symptom of depression, and with restlessness. Both the ADHD and the schizophrenia PGSs were also linked to depression symptoms, such as tiredness, appetite and sleep problems.

Taken together, these results suggest that genetic risk does not neatly map onto diagnostic constructs, as PGSs derived from GWASs of specific traits were associated with cross-trait indicators. In fact, genetic studies consistently show that comorbid disorders are genetically correlated (Martin et al., 2018), and that PGSs for mental health disorders are associated with phenotypes that frequently co-occur. For example, depression and anxiety are genetically correlated (Purves et al., 2020), and PGSs for depression are associated with comorbid conditions, such as anxiety and substance use disorder (Andersen et al., 2017; Gurriarán et al., 2019; Shi et al., 2022).

Focusing on individual symptoms provided additional evidence that the genetic risk for a disorder may not be universally associated with all components of commonly comorbid disorders. In other words, genetic correlations between disorders may be driven by influences on specific symptoms, rather than entire conditions. For example, the genetic correlation between depression and ADHD may be primarily attributable to genetic influences on somatic symptoms, as shown in Chapter 3. Furthermore, the genetic predisposition to non-psychiatric traits, such as BMI and educational attainment, may contribute to comorbidity by affecting symptoms across disorders. For example, the BMI PGS was linked to being bullied in childhood (Chapter 2), which suggests a gene-environment correlation (Schoeler et al., 2019). Children predisposed to a higher BMI may experience negative reactions from their peers (Avinun & Hariri, 2019; Davidson & Demaray, 2007), which may, in turn, contribute to the development of depression (i.e., evocative gene-environment correlation).

Similarly, phenotypic associations between comorbid disorders may be driven by specific symptoms under genetic influence. The association between the PGS for ADHD and restlessness (Chapter 3), though not surprising, may indicate a biologically meaningful pathway: for example, the genetic predisposition to ADHD might contribute to restlessness in depression, partially explaining the co-occurrence of the two disorders. However, this is complicated by the ubiquity of depression symptoms across psychopathology (Forbes et al., 2023), as well as the overlap of depression symptoms and those of ADHD. The current classification system, where overlap between different conditions is frequent, makes it complicated to

determine whether phenotypic and genetic comorbidity reflect shared pathways between different conditions, or simply measurement issues.

In summary, my results demonstrate how comorbidity may be symptom-driven rather than disorder-driven. Traditional sum-score approaches fail to reveal symptom-specific insights, thus hiding potentially useful information that could help explain the emergence of comorbidity. Considering individual symptoms in genetic analyses may provide a more accurate picture of comorbidity within the genetics of depression.

5.2.3 Genetic risk is associated with trait-relevant symptoms

Building on the idea that comorbidity may be symptom-driven, it is important to highlight that genetic risk is not only associated with sum-scores measuring individual disorders, as suggested by previous research, but also with specific trait-relevant symptoms, as shown in this thesis. The PGS for depression was associated with a single symptom – anhedonia – in Chapter 2. Similarly, the PGS for ADHD was linked to symptoms such as restlessness (Chapter 3) and being easily distracted (Chapter 2). Overall, these findings are consistent with genetic studies that report associations between PGSs and their corresponding phenotypes (Demontis et al., 2019; Howard, 2019). These results also align with a previous study on networks and PGSs, which found that the PGS for schizophrenia was associated with positive (but not negative) symptoms of the disorder (Isvoranu et al., 2020).

This thesis contributes to the literature by suggesting that specific symptoms may drive the associations between genetic risk and phenotypes. For example, the association between the depression PGS and phenotypic

depression may be primarily driven by anhedonia in childhood. Similarly, the association between the ADHD PGS and phenotypic ADHD may be largely explained by symptoms such as restlessness and being easily distracted, rather than by symptoms of impulsivity. These findings offer further evidence that genetic risk may influence specific symptoms, rather than universally affecting a disorder. This notion challenges the traditional comorbidity model by proposing that there is no genetic predisposition to distinct, co-occurring disorder entities, but rather a genetic predisposition to individual symptoms.

It is worth noting that there were differences in the patterns of associations of the polygenic risk for depression in Chapters 2 and 3. In Chapter 2, the depression PGS was associated exclusively with anhedonia, whereas in Chapter 3, it was associated more broadly with all symptoms of depression and anxiety. Several factors may explain these discrepancies. In particular, there are a number of methodological differences between the analyses in the two studies. For example, while Chapter 3 employed mediation analysis, Chapter 2 used network analysis, which typically focuses on identifying sparse networks, for example by pushing small edge weights towards zero with regularisation (Appendix A, Supplementary Methods) (Epskamp & Fried, 2018). This approach simplifies complex patterns of associations, minimises overfitting, and maximises generalisability. Since the cross-domain correlations between PGSs and symptoms were smaller than within-domain correlations between symptoms, network regularisation may have led to fewer connections between PGSs and questionnaire items in Chapter 2.

In addition, while Chapter 2 focused on children, Chapter 3 involved a sample of adults. The PGSs used in both studies were derived from GWASs summary statistics of adult participants, which could have maximised their predictive power in an adult sample, leading to more associations with individual symptoms in Chapter 3. Indeed, evidence suggests that DNA-based genetic effects for childhood problems may be especially low (Cheesman et al., 2017). Additionally, psychiatric PGSs are typically based on GWASs of disorders (e.g., where cases are compared to controls). When derived from GWASs with large enough samples, PGSs would capture effects for all components of a disorder (e.g., tiredness and concentration problems), as they feature in GWASs selection criteria.

Although the findings in Chapter 2 were replicated in an independent cohort, Chapter 3 included a larger sample, offering more power to detect the small effect sizes of PGSs. Furthermore, Chapter 2 used a set of questionnaires that measured children's behavioural and emotional difficulties (i.e., SMFQ and SDQ), while Chapter 3 focused on clinically oriented measures of depression and anxiety (based on PHQ-9 and GAD-7). These differences make the two studies less comparable, as they use different variables – an important consideration when employing network analysis.

There may also be a theoretical reason for the contrasting results. This explanation draws on the concept of causal reciprocal relationships between symptoms, which is central to network theory: symptoms of depression and anxiety are proposed to causally influence each other (Borsboom, 2017). These direct causal associations may, over time, induce genetic correlations

between symptoms that were previously unrelated (Sluis et al., 2010). Indeed, when not adjusting correlations for all symptoms in networks in Chapter 2 (i.e., in covariate-adjusted correlations), I observed similar correlation estimates between the PGS for depression and all depression symptoms. PGSs would not effectively differentiate between unmediated genetic effects on individual symptoms, and mediated genetic effects that operate through symptom-symptom relationships. For example, the genetic risk for depression may influence tiredness, which, in turn, may increase concentration problems, creating an association between the genetic risk for depression and concentration problems, which acts via tiredness. This process may unfold over development and be less prominent in children compared to adults, whose depression symptoms are more established and entrenched in their patterns of association.

5.2.4 Section summary

Overall, the symptom-based approach adopted in this thesis suggests that genetic, neurobiological, and treatment-related factors may be best understood at the symptom level. This approach provides new insights into comorbidity, highlighting that it may be symptom-driven and influenced by genetic and neurobiological factors that span across traditional diagnostic boundaries.

5.3 Somatic symptoms of depression: a unique genetic, neural, and pharmacological profile

Interestingly, somatic symptoms of depression and anxiety (i.e., tiredness, sleep problems, appetite and libido issues) appeared to have a unique pattern

of relationships with the genetic propensity to psychiatric and non-psychiatric traits, neural markers, and response to sertraline. Specifically, tiredness was associated with the PGSs for depression and ADHD and with volumes of the insula, cingulate and mOFC, while sleep problems were associated with the PGSs for depression and ADHD, and volumes of mOFC and cingulate (Chapter 3). Appetite issues were associated with the PGSs for depression and ADHD and volumes of the cingulate and mOFC (Chapter 3). I found a negative association between the PGS for educational attainment and frequent complaints of sickness in 11-year-old children (Chapter 2). Lastly, sertraline increased tiredness, appetite and libido problems after 2 weeks of treatment, and increased sleep and appetite issues after 6 weeks of treatment (Chapter 4).

This pattern of findings suggests that somatic indicators may represent a distinct subgroup of depression and anxiety symptoms, which differs from others in how susceptible they are to the influence of genetics, neurobiology and pharmacological treatment.

5.3.1 Somatic symptoms are more prevalent and less specific

Notably, the somatic symptoms of depression included in these analyses are often shared across a variety of mental health disorders. Insomnia, fatigue, decreased appetite and weight gain, for example, rank among the top 20 symptoms that repeat across DSM chapters (Forbes et al., 2023). Moreover, somatic symptoms of depression overlap with those seen in physical conditions. Tiredness, for instance, is a common complaint in primary care and

can signal a variety of issues, including anaemia, diabetes, thyroid disease and autoimmune disorders (Moncrieff & Fletcher, 2007). This overlap is unsurprising and may reflect somatic symptoms as general indicators of both physical and psychological distress. In other words, somatic symptoms in psychopathology may be akin to headaches or abdominal pain in general medicine – indicating something is wrong, but not pointing to a specific disorder.

Perhaps because of this non-specificity, somatic symptoms are frequently reported in clinical samples. Early evidence suggests that tiredness and sleep problems are among the most frequently reported symptoms of depression in primary care (Tylee et al., 1999), alongside low mood. Fried and Nesse (2015) report that mean levels of difficulties with sleep during the night are comparable to mean levels of sadness in a sample of ~3,500 depressed participants from the STAR*D trial (Fried & Nesse, 2015). Somatic complaints may be especially prevalent in population-based cohorts. For example, Thorp et al. (2020) found that ~48% of a sample drawn from the UK Biobank reported sleep problems and fatigue, compared to ~22% reporting depressed mood and ~18% reporting anhedonia (Thorp et al., 2020). These patterns are reflected in the higher mean levels of somatic symptoms than other symptoms observed in the UK Biobank sample used in Chapter 3. Notably, although somatic symptoms may be more frequently reported, some evidence suggests that they do not correlate highly with depression severity (r<0.07, compared to the highest correlation, between suicidal thoughts and severity, r=0.31) (Zimmerman et al., 2018) and functional impairment (Fried & Nesse, 2014).

5.3.2 Somatic and psychological symptoms of depression

Somatic symptoms may not only be more prevalent in clinical and population-based cohorts, but they may also differ in significant ways from other symptoms of depression, which can be referred to as “psychological” symptoms. Patients may find it easier to express concerns over physical functions, such as sleep disturbances and fatigue, than to disclose more distressing psychological symptoms like suicidal thoughts or feelings of worthlessness. This is particularly relevant in primary care settings, where patients may be more inclined to report physical symptoms. Additionally, depression manifests differently across cultures, age groups, and other sociodemographic contexts, meaning that attitudes towards somatic symptoms may also vary (Goldberg & Bridges, 1988; Goodmann et al., 2021; Kessler & Bromet, 2013; Lewis-Fernández & Kleinman, 1995).

While the construct of depression is context-dependent, the psychometric instruments used to measure it may also not apply universally. For example, commonly used depression measures often do not show measurement invariance across different populations (Baas et al., 2011; Crockett et al., 2005; Nguyen et al., 2004; Williams et al., 2007), meaning they may not consistently measure the same construct across different groups. As a result, self-reported depression symptoms may vary depending on the context in which they are measured. Somatic symptoms, which are more concrete and universally recognizable, may be measured more reliably than psychological symptoms, potentially inflating estimates of associations with neurobiological markers. Additionally, current depression scales may not adequately capture important phenomenological aspects of depression, such

as depersonalisation (Kendler, 2016), and often fail to distinguish fatigue from anergia (i.e., tiredness in the absence of exertion).

5.3.3 Intentionality in psychological symptoms

Psychological symptoms can be conceptualised as mental states, such as beliefs, emotions, and desires (Borsboom et al., 2019). These mental states have "intentional content" – meaning they are directed at or about something. For example, a depressed individual may hold beliefs about themselves (e.g., "I am worthless"), the world (e.g., "The world is a hopeless place") and the future (e.g., "Things will not improve"), which may also shape their desires (e.g., leading to thoughts of death). Mental states are "multiply realizable": there are many ways in which a person can feel worthless or hopeless, with no single manifestation of these feelings (i.e., intentional content) having a privileged role (Borsboom et al., 2019). Realisations of mental states may differ across individuals, time, and context.

In contrast, somatic symptoms do not seem to have intentional content (i.e., they are not about something) and may be driven by uniform underlying biological mechanisms (Borsboom et al., 2019). For example, insomnia has a limited number of possible manifestations (e.g., difficulty falling asleep or staying asleep) and reliably leads to fatigue. This may explain the recurrent pattern of associations between somatic symptoms and neurobiological markers observed in this thesis.

Focusing on neurobiological correlates of bodily states, rather than mental states, may yield clearer insights into the biological mechanisms of depression. For example, somatic symptoms have been shown to be

associated with higher levels of inflammatory markers than other symptoms (Milaneschi et al., 2021; Pariante, 2021; Penninx et al., 2025). In particular, recent meta-analytic evidence points towards a specific subpopulation of depressed patients with increased C-reactive protein (CRP) levels and higher levels of problems with appetite, tiredness, sleep, and volition (Frank et al., 2021). However, as previously noted, these symptoms are very common, and not specific to mental health disorders, leading to a potentially spurious co-occurrence of inflammation and depression, mostly driven by over-general somatic symptoms.

Similarly, a recent GWAS of individual depression symptoms (Thorp et al., 2020) found appetite problems to be the symptom with the highest SNP-heritability, estimated to be ~9%, compared to the SNP-heritability of the depression sum-score, estimated to be ~6%. This study additionally used genomic SEM, a method that utilises a genetic variance-covariance matrix derived from GWASs summary statistics to analyse the genetic architecture of comorbid traits. Interestingly, psychological and somatic symptoms loaded onto separate factors, reinforcing the idea that these two symptom clusters may have distinct biological mechanisms.

5.3.4 Section summary

Overall, the findings discussed in this section suggest that somatic symptoms of depression, such as tiredness, appetite changes and sleep disturbances, may have different biological underpinnings compared to psychological symptoms like feelings of hopelessness and worthlessness. Somatic symptoms appear to be more prevalent, a factor that may be influenced by the

complexities of the conceptualisation and measurement of depression across contexts.

5.4 Informing psychiatric nosology with symptom-based approaches

The findings presented in this thesis suggest that a symptom-based approach may provide a more nuanced understanding of mental health disorders than categorical diagnoses. These insights can inform psychiatric nosology by redefining how disorders are categorised, conceptualised and measured, ultimately contributing to a more precise classification, grounded in aetiology. A classification system for mental health problems should adequately account for heterogeneity, comorbidity, and transdiagnostic biological processes, as well as discriminate effectively between different conditions (Dalgleish et al., 2020; Fried, 2022). In this section, I examine the historical lack of theory at the basis of current classification systems, the utility (or otherwise) of diagnoses, and an alternative, system-based approach to nosology.

5.4.1 A theory-driven aetiological perspective on psychiatric nosology

Symptom heterogeneity would not pose as much of a challenge to research if depression reflected a single, unitary disorder. By way of comparison, in physical medicine, overlapping symptoms do not always inflate comorbidity, as disorders can be distinguished through objective biomarkers. For example, streptococcal pharyngitis (strep throat) and viral sore throat share symptoms such as fever, swollen tonsils, and difficulty swallowing. However, a throat swab can easily differentiate bacterial from viral infections. In contrast, efforts

to identify a unique genetic or neurobiological biomarker for depression have largely been unsuccessful, suggesting that it may instead encompass multiple distinct conditions, rather than a single disorder. This reinforces the need for a classification system that accounts for heterogeneity and is informed by aetiological mechanisms.

In the absence of objective tests or indeed a mechanistic definition for depression, research has relied on symptom-based definitions, and typically operationalises depression through diagnostic criteria, such as those outlined in the DSM. However, the development of diagnostic criteria was not theory-driven. For example, the DSM-III was influenced by the work of American psychologist John Feighner in the 1970s (Feighner et al., 1972; Kendler et al., 2010), who, in turn, drew from the work of Cassidy and colleagues in the 1950s (Cassidy et al., 1957). While these criteria were among the first efforts to classify mental health disorders based on empirical evidence, they were also shaped by context and clinical intuition. A notable example is Cassidy's recollection of setting the threshold of a depression diagnosis at six out of ten symptoms because "it sounded about right" (Kendler et al., 2010). Similarly, widely used depression scales, such as the Hamilton Depression Rating Scale, were developed primarily based on clinical experience rather than informed by a coherent theory of depression (Fried et al., 2022).

The development of standardised criteria and scales for depression represents a significant contribution to the history of psychiatry and evidence-based practice. However, the lack of consideration for aetiology in psychiatric nosology has far-reaching consequences for research. For instance, there is

no clear rationale for why genetic or neurobiological factors should align neatly with the diagnostic criteria for depression, given that they do not feature in its definition. Improving the classification of mental health disorders may require incorporating an aetiological perspective (Fried, 2020), which would involve having explicit theories about the nature of these conditions, as well as adhering to modern best practices.

The limitations of current classification systems have been widely discussed, and alternative solutions have been proposed (Eaton et al., 2023). For instance, the Research Domain Criteria (RDoC) framework aims to move beyond symptom-based diagnoses toward a biologically informed understanding of mental health problems (Cuthbert, 2014; Insel et al., 2010; Morris et al., 2022). RDoC emphasises the importance of integrating different levels of analysis in a unified framework to identify distal and proximal causes of mental health disorders. Additionally, data-driven approaches have been developed based on empirical evidence. For instance, the Hierarchical Taxonomy of Psychopathology (HiTOP) organises dimensions of mental health problems by identifying patterns of covariation between symptoms, forming a hierarchy from symptoms to broader spectra (Kotov et al., 2021). HiTOP and similar models are inherently transdiagnostic and account for observed comorbidity patterns. However, despite their ability to accurately describe psychopathology at a dimensional level, these frameworks largely rely on psychometric factors, whose interpretation remains contested (Fried et al., 2021; van Bork et al., 2017).

Overall, classification helps summarise and communicate information about patterns of behaviour, cognition, and emotions. When classification proves to be complex, as in psychiatry, multiple classification systems may be used effectively for different aims (P. J. Jones & Robinaugh, 2021). For example, one framework may be more effective for evaluating treatment, while another may be better suited to exploring the aetiology of mental health disorders. A parallel can be drawn from biology, where species pluralism suggests that different definitions of “species” are useful depending on the objective (Dupré, 1999). Similarly, psychiatry may benefit from the use of a flexible approach to classification.

5.4.2 ‘Lumping’ and ‘splitting’

It is important to recognise that diagnostic criteria can be valuable to public health and policy research. For example, standardised criteria can help estimate the prevalence of mental health disorders within a population. Similarly, sum-scores can have clinical utility, informing the choices of patients, clinical professionals, and insurance providers, as well as providing a way of monitoring the progression of illness and guiding treatment selection. However, an overreliance on diagnostic criteria may lead to an unjustified reification of diagnostic categories – that is, treating the abstract concept of diagnosis as a tangible, material entity. While mental health problems can be described using diagnostic labels, and these descriptions serve important functions in research and practice, mental health problems are not diagnoses in a literal sense (Borsboom et al., 2019, 2022; Fried, 2022).

In contrast, symptoms can be more directly mapped onto observable phenomena, without the need to postulate latent, unmeasurable constructs. The existence of latent factors, such as Major Depressive Disorder or the p-factor, requires an explanation (it is an *explanandum*), it does not inherently provide an explanation for observable phenomena (it is not an *explanans*) (Fried et al., 2021). As shown in Chapters 2 and 3, neurobiological and genetic factors can have differential associations with individual symptoms that move beyond diagnostic constructs. Chapter 4 highlighted how the heterogeneity of symptoms of depression and anxiety may explain some of the puzzling findings in the antidepressant literature. This suggests that symptom heterogeneity may be a valuable tool in depression research. By focusing on more granular phenotypes that extend beyond traditional disorder categories, research may identify transdiagnostic indicators under genetic or neurobiological influence (Tiego et al., 2023).

However, the strategy of focusing on individual components may not be fruitful when investigating links between neurobiological and genetic factors. For example, in Chapter 3, examining the volumes of individual brain areas did not appear to provide additional information on the effects of genetic risk on brain morphology. This may be because genetic influences are distributed more diffusely across the brain, or affect cell types, receptors, neurotransmitter function or activation instead. Identifying the most informative level of analysis for capturing associations across levels of organization, such as between genetic and neurobiological levels, requires further investigation.

5.4.3 The importance of symptom-symptom associations: towards systems-based thinking

While a focus on symptoms can provide valuable insights into the causes and consequences of depression, the findings in this thesis highlight the importance of also examining relationships between symptoms. In Chapter 2, PGSs were associated with a broader set of items in covariate-adjusted correlations than in network analyses, which account for the interconnections between network nodes. Similarly, Chapter 4 showed that sertraline had rapid effects on depression symptoms compared to placebo, but its effects were only detected when taking into account both cross-sectional and longitudinal symptom associations. However, sertraline did not seem to affect network structures, indicating that treatment may affect individual symptoms, but not the relationships between them.

These findings suggest that future research should account for the dynamic interactions between symptoms, aligning with the concept of reciprocal causal relationships between symptoms, which is central to network theory (Borsboom, 2017). Network theory is a systems-based approach that conceptualises mental health disorders as emergent properties arising from interactions between symptoms. More broadly, a systems-based approach explicitly models the interactions among a set of components across time and levels of analysis, aiming to capture the complexity of real-world systems (e.g., the weather or the stock market) (Borsboom et al., 2022; Fried, 2022). A useful analogy is the murmuration of starlings, a large group of birds that fly in a synchronised pattern. This type of flocking is an emergent phenomenon, and it cannot be understood by studying individual birds, isolating elements of the

system. Similarly, mental health disorders may not be fully explained by examining symptoms independently, without considering their interdependence (Ebrahimi et al., 2024).

Thinking of mental health problems as systems has two main implications relevant to the work presented in this thesis. First, a systems-based perspective challenges the idea that symptoms have epistemic superiority in research (Fried, 2022) – that is, symptoms do not necessarily provide better knowledge than genetic and neurobiological factors. Instead, systems-based approaches emphasise interactions between levels of explanation (e.g., biological, psychological, social). Future research should integrate genetic and neurobiological measures in symptom-level analyses, such as network analyses, as shown in this thesis. Additionally, studies should investigate how genetic risk and neurobiological factors influence symptom relationships, such as whether there is a genetic predisposition to highly interconnected symptom networks.

Second, shifting the focus to interactions between symptoms helps resolve the tension between disease-modifying and symptom-modifying treatment processes. Some treatments can alleviate symptoms without addressing underlying causes. For example, calcium channel blockers are commonly used to treat high blood pressure. Although effective at lowering blood pressure, they do not target potential causal factors, such as diabetes. By contrast, disease-modifying drugs are preferable (e.g., targeted modern chemotherapy for cancer). Psychiatric medications are often criticised for only temporarily alleviating symptoms, rather than addressing the underlying,

latent disorders (Ghaemi, 2022). However, if mental health disorders are conceptualised as emergent properties of interacting symptoms, then treating symptoms directly modifies the disorder itself.

5.4.4 Section summary

Defining depression and other mental health disorders through symptom-based diagnoses, in the absence of biomarkers, poses a significant challenge for psychiatric research and classification. However, symptoms have the unique advantage of mapping more neatly onto observable reality than latent disorder constructs. This makes symptoms particularly useful for identifying biomarkers and informing psychiatric nosology with theory-driven aetiological considerations. An alternative to traditional classification frameworks is a systems-based perspective, which conceptualises mental health disorders as emerging from the interactions between symptoms.

5.5 Reflections on the Involvement of Lived Experience Experts

Lived experience refers to the knowledge and insight gained through first-hand experiences of mental health challenges. Recent shifts in mental health research have increasingly recognised the value of lived experience, acknowledging that different types of evidence have the potential to improve the quality and expand the scope of mental health science (Wellcome, 2025). In line with this, the National Institute for Health and Care Research (NIHR) has established principles that prioritise working 'with' members of the public, rather than conducting research 'for' them (NIHR, 2025). This approach reflects fundamental principles of democracy and citizenship: people who are affected by research in mental health have a right to have a say in it (NIHR, 2025). Lived experience experts (LE experts) provide their expertise, insights and personal knowledge to inform all aspects of the research process, including identifying priority areas, shaping design and governance, contributing to analysis, and guiding dissemination strategies (Fusar-Poli et al., 2023). Their involvement ensures that research is more inclusive and relevant to those it aims to help.

The research presented in this thesis was conducted as part of the UCL-Wellcome PhD programme in Mental Health Science. Part of the programme's ethos is the co-production of research with people with lived experience of mental illness. Students receive training in co-production and aim to include LE experts in the PhD research process. Each student is supported by a thesis committee meeting that includes LE experts alongside academic supervisors.

For this PhD project, two experts with a lived experience of depression and/or anxiety took part in biannual thesis committee meetings.

Each chapter of the thesis was discussed with in thesis committee meetings, which addressed aspects of the research design, rationale, theoretical framework, and interpretation and implications of findings. These meetings acted as a space for collective problem-solving and iterative knowledge exchange. At times, this process felt experimental, one that focused more on the imperfect but real practice of co-production than on identifiable contributions to the PhD research. Nevertheless, it provided a valuable model for embedding lived experience in PhD projects.

Three key areas of the research particularly benefited from the input of LE experts. First, the conceptual framework of network theory seemed to resonate with LE experts. Specifically, both experts felt that the idea of symptoms in mutual, dynamic causal relationships reflected their lived experience. Second, one LE expert drew on their experience of the side-effects of SSRIs, reiterating the importance of considering the physical dimensions of depression, as explored in Chapter 4. Third, one LE expert provided insightful feedback on the methods used in this thesis, contributing both their lived experience and their knowledge of mathematical modelling. This highlights the diverse ways in which co-production can improve basic science, showing that lived experience and scientific expertise are not mutually exclusive.

The inclusion of LE expert in the thesis committee was grounded in principles of co-production. However, future involvement efforts should be

expanded to achieve meaningful participation across all aspects of research. For example, meaningful co-production would involve recruiting a larger, more diverse group of LE experts to contribute to all key decisions (e.g., co-applying for funding, designing studies, disseminating findings) (NIHR, 2025). While this type of comprehensive involvement was outside of the scope of this PhD (partly due to systemic limitations and the constrained agency of early-career researchers), it remains a critical goal. In particular, involving LE experts in PhD-level research would particularly benefit the designing state (e.g., co-developing of PhD studies) and dissemination efforts (e.g., co-writing of papers and blog posts).

5.6 General limitations

The findings presented in this thesis should be considered in light of key limitations. While each chapter details study-specific limitations, this section addresses overarching limitations across all three studies. In particular, I discuss confounding, measurement error, reproducibility, small effect sizes, selection and attrition bias, and the limited explanatory insights of these findings.

5.6.1 Unobserved confounders

Identifying the complex causes of mental health disorders is a fundamental aim of psychiatric research. However, causal inference in genetic and epidemiological studies is hindered by confounding (Pingault et al., 2018), which occurs when a variable causally influences both an exposure and an outcome, creating a spurious association between them. In observational studies, unobserved confounders can lead to incorrect estimates of effects (Nørgaard et al., 2017).

This issue is particularly relevant in network analysis, which estimates and visualises relationships between symptoms. Failing to account for a common cause or an influential symptom may alter network structures, leading to inaccurate conclusions and highlighting the importance of careful variable selection (Borsboom et al., 2021). In Chapters 2, 3 and 4, I used widely adopted questionnaires to measure emotional and behavioural problems in childhood, as well as depression and anxiety in adulthood, while controlling for key confounders (e.g., sex and age). Nonetheless, the potential

influence of unknown or unmeasured confounding variables cannot be ruled out.

5.6.2 Measurement error

Symptom-level analyses rely on the assessment of individual symptoms, which in this thesis were operationalised as single items from scales measuring mental health and related traits. However, using single-item measures can introduce measurement error (i.e., a difference between the true value and the measured value of a variable). For example, to measure the symptom of tiredness in Chapters 3 and 4, I used scores on the self-reported item “Feeling tired or having little energy” over the last two weeks. Because symptom-level analyses are less common than sum-score analyses, more precise measures of symptoms remain limited. Future research should aim to reduce measurement error in symptom-level analyses, for example, through repeated symptom assessments, or by using SEM to construct factor scores from multiple measurements of symptoms, potentially integrating factor and network approaches (Epskamp, 2020).

Measurement error also presents a significant challenge in polygenic scoring. PGSs are dependent on the power of the corresponding GWAS, with larger GWASs yielding more predictive scores. PGSs only partially capture (SNP-based or twin-based) heritability and are an imperfect measure of the genetic liability to a trait (Allegrini et al., 2022; Pingault et al., 2022). The gap between heritability estimates and the variance explained by PGSs can be understood in terms of measurement error (Pingault et al., 2021; Tucker-Drob, 2017). This limitation could account for some of the null findings in this thesis,

such as the lack of associations between the PGS for depression and brain structure in Chapter 3, or the associations of PGSs with relatively few symptoms in Chapter 2. Future studies should consider recently developed methods (e.g., *GSens*) that partially account for measurement error in polygenic scoring (Pingault et al., 2021).

5.6.3 Small effect sizes

The estimates of associations between symptoms and PGSs, brain structures and treatment observed in this thesis are small or minimal according to conventional standards. However, the order of magnitude of these associations aligns with effect sizes reported in research on PGSs (Howard et al., 2019), and in network studies of brain structure (Freichel et al., 2024), and SSRIs (Boschloo et al., 2023).

Importantly, small associations can play a meaningful role in explaining complex psychological phenomena. In fact, small genetic and neurobiological effects highlight the multi-factorial nature of mental health disorders, with research now adopting a sceptical stance towards large effect sizes. Moreover, small effects can have significant public health implications, as their impact accumulates over time and at scale (Carey et al., 2023; Götz et al., 2022.). In particular, small shifts in effect sizes (such as small improvements with sertraline treatment) may disproportionally impact the tail end of the distribution, affecting those with the most severe cases of mental health disorders to a greater extent (Carey et al., 2023).

5.6.4 Attrition and selection bias

Bias in research refers to the systematic introduction of error that can lead to certain outcomes being favoured over others (Pannucci & Wilkins, 2010). Some degree of bias is inevitable in research, and population-based cohorts are typically influenced by various types of biases. These can include sampling bias, which occurs when the sampled population is not representative of the target population, and attrition bias, which results from the systematic loss of participants over time. In Chapters 2 and 3, I used data from large population-based cohorts (ALSPAC, TEDS and UK Biobank). While ALSPAC and TEDS are broadly representative of the UK population (Boyd et al., 2013; Fraser et al., 2013; Rimfeld et al., 2019), they are nonetheless affected by selective attrition, which may limit the generalisability of findings.

Additionally, the UK Biobank is affected by sampling bias, as its participants are on average older, healthier and better educated than the general UK population (Fry et al., 2017). This can have important downstream consequences for research. For example, a recent study showed that participation bias in UK Biobank can affect genetic findings (Schoeler et al., 2023). This issue is likely exacerbated in the subsample of participants who underwent imaging scans (Lyall et al., 2022). Several solutions have been proposed to effectively mitigate attrition and sampling bias, such as sampling weights (Schoeler et al., 2023). Notably, in contrast to Chapter 3, Chapter 4 used data from a randomised controlled trial (Lewis et al., 2019). By matching participants on key confounders at baseline, and randomising them to treatment groups, this design helps minimise sampling bias and strengthens causal inference.

Importantly, most genetic studies, including Chapters 2 and 3, exclude participants of non-European ancestry. A wealth of research demonstrates that genetic findings in European ancestry populations are not systematically portable to other ancestries (Bitarello & Mathieson, 2020; Cavazos & Witte, 2021; Duncan et al., 2019; Privé et al., 2022). Besides being a fundamental issue of equity, this limitation affects the generalisability of genetic findings, as the majority of the global population is excluded (Bustamante et al., 2011; Fatumo et al., 2022). Recent efforts to mitigate this issue include multi-ancestry GWASs (Friligkou et al., 2024; McIntosh et al., 2024; Meng et al., 2024; Nievergelt et al., 2024), and methods dedicated to polygenic scoring in admixed-ancestry samples (M. Cai et al., 2021; Ruan et al., 2022; Zhang et al., 2023). To improve the robustness and generalisability of the findings of this thesis, future research should prioritise replication in more ancestrally diverse samples, as well as in samples with improved representativeness and higher retention rates.

5.6.5 Limited explanatory insights

Network analysis is typically used in an exploratory, hypothesis-generating way, and the studies in this thesis are no exception (e.g., Chapters 2 and 4). However, where possible, exploratory approaches were complemented by confirmatory analyses, such as the replication of primary findings in an independent sample in Chapter 2. In Chapter 3, I employed a more directional mediation approach to test specific pathways.

Nonetheless, this work does not provide conclusive evidence against or in favour of either network theory or the common cause model, and this was

indeed not an aim of this thesis. Disentangling these theories requires formulating clear, testable predictions (Fried, 2020). In particular, identifying causal relationships between symptoms and testing them through experimental manipulation could provide more direct evidence for network theory. For example, if sleep problems are hypothesised to cause tiredness, an optimal (although practically challenging) test would involve directly intervening on sleep with a symptom-specific treatment and observing its effects on tiredness.

A similar limitation applies to PGSs, which aggregate the effects of many genetic variants (and are, in a sense, sum-scores), but do not, on their own, explain how genetic variation leads to differences in behavioural traits. Additionally, PGSs can be affected by confounding factors such as assortative mating, population stratification and gene-environment correlation (as can other variables across the behavioural sciences) (Pingault et al., 2022). Therefore, their primary value may lie in prediction rather than explanation (Plomin & Stumm, 2021). However, increasing the predictive power of PGSs requires large GWASs sample sizes, which are often obtained by using broad disorder definitions, at the cost of phenotypic precision. Larger genetic datasets enable the identification of novel genetic risk loci, but they also introduce greater heterogeneity (N. Cai, Choi, et al., 2020), complicating efforts to refine psychiatric classification with aetiologically-informed evidence.

5.6.6 Section summary

The influence of unobserved confounders, measurement error, attrition bias, and selection bias need to be considered as a potential alternative explanation

to the findings of this thesis. Other important considerations include the small effect sizes of most reported associations and limited explanatory insights.

5.7 Implications for research and clinical interventions

This thesis showed that individual symptoms of psychopathology are differentially associated with genetic risk, brain phenotypes, and treatment response. These findings have implications for both research and clinical interventions.

5.7.1 Implications for research

The findings of this thesis suggest that studying the genetic and neurobiological bases of diagnostic labels, and taking them to be fixed biological entities, may hinder efforts to identify biomarkers for depression and other mental health disorders. For example, while GWASs rely on DSM-based diagnoses (Wray et al., 2018), it remains unclear whether these phenotypes are the most suitable for genetic discovery. A symptom-level approach, alongside traditional sum-scores, may allow research to move beyond diagnostic constructs and identify transdiagnostic indicators that more accurately reflect underlying biological mechanisms. A granular approach to phenotyping, such as GWASs of individual symptoms (Thorp et al., 2020), could be instrumental, especially when combined with efforts to mitigate measurement error in symptom-level analyses.

Additionally, this thesis highlights the importance of understanding mental health disorders as complex dynamic systems (Borsboom et al., 2022; Fried, 2022). Future research should focus on theoretical development and causally informative designs (e.g., experimental manipulation of individual symptoms to establish causation). Investigating interactions between

symptoms over time may benefit from complementing longitudinal panel data with experience sampling methods, which allow for the study of symptom fluctuations over shorter time intervals (Bos et al., 2017).

5.7.2 Implications for clinical interventions

The findings of this thesis support the idea of targeting individual symptoms in treatment. Clinicians and patients may collaboratively identify and address key symptoms to target, rather than treat disorders as uniform entities. This approach could help refine and personalise treatment strategies. Notably, Chapter 4 highlighted the early beneficial effects of sertraline on core symptoms of depression, as well as its detrimental effects on somatic symptoms. Therefore, it is important to acknowledge the temporary worsening of somatic symptoms when making decisions on the use of SSRIs, as well as highlighting the potential for a rapid effect on mood.

From a therapeutic perspective, functional analysis aligns with systems thinking and network theory, as it considers the patient's behaviours, thoughts, emotions, and relationships among them (Yoman, 2008). Similarly, process-based therapy highlights the complex, interacting factors in a patient's life, over fixed diagnostic criteria (Hofmann & Hayes, 2019). These approaches inherently account for comorbidity, considering it a natural consequence of symptoms influencing one another over time.

In summary, adopting a more nuanced, symptom-focused perspective to both research and clinical practice may significantly improve our understanding of the aetiology of mental health disorders, refine their classification and lead to personalised treatment options.

5.8 Conclusion

In summary, this thesis took a symptom-level approach to psychopathology, with a particular focus on depression. I examined symptom-specific associations with genetic risk, brain structure, and sertraline treatment. My main findings indicate that: (i) polygenic scores for depression and related traits are associated with specific subsets of psychopathology symptoms; (ii) regional brain volumes are differentially associated with individual symptoms; and (iii) sertraline has rapid beneficial and detrimental effects on individual symptoms of depression and anxiety. This work suggests that aggregating heterogeneous symptoms into summary scores can hide meaningful information on the genetic aetiology, brain mechanisms and treatment response of depression and other disorders. Focusing on individual symptoms can yield new insights into comorbidity and inform future developments in psychiatric nosology.

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Appendices

Appendix A – Supplementary Material for Chapter 2

Supplementary Methods

Quality control for PGSs

I performed standard quality control procedures on GWAS summary statistics and target data (Choi et al., 2020). When the information was provided by GWAS authors, SNPs with INFO scores below 0.8 and Minor Allele Frequency (MAF) below 0.01 were excluded, along with ambiguous and duplicate SNPs (see Appendix A, Supplementary Table 2). ALSPAC provides genotype information for children of European ancestry (as detailed here

https://www.bristol.ac.uk/media-library/sites/alspac/migrated/documents/gwas-data-generation.pdf?u07022013) and TEDS provides genotype data for children of white ethnicity (as detailed here

https://datadictionary.teds.ac.uk/exclusions.htm). The analysis was therefore restricted to these participants.

In ALSPAC genetic data, I removed non-autosomal SNPs, as well as SNPs and individuals with high levels of missingness (more than 5% missing). Related individuals (10% or more alleles shared Identity By Descent), individuals with discordant sex information and heterozygosity rate more than 3 standard deviations from the mean were excluded. SNPs with a MAF<0.01 and significantly deviating from Hardy-Weinberg Equilibrium (p<1e-7) were excluded, leaving 4,886,821 SNPs. We calculated polygenic scores by filtering

HapMap3 SNPs and computing a Linkage Disequilibrium (LD) reference from our data (Privé, 2022). In TEDS, UK Biobank was used as LD reference (Privé et al., 2022).

PGS calculation

PGSs were calculate with LDPred2, a Bayesian method to derive polygenic scores using information on genetic architecture (SNP-heritability), on the fraction of causal variants (polygenicity) and on LD obtained from a reference panel (Privé et al., 2020).

Target data (ALSPAC and TEDS) were used as reference LD panels in PGS calculations. PGSs were generated by using the option 'LDPred2-auto'. To compute PGSs, the recommended steps by the LDPred2 development team (Privé, 2022) were followed, and, accordingly, variants included were restricted to HapMap3 variants

(https://www.sanger.ac.uk/resources/downloads/human/hapmap3.html). Example code is available on GitHub

(https://github.com/giuliapiazza18/Unweaving-the-polygenic-web-pipeline).

Network estimation

Unregularised model search was used for network estimation ('ggmModSelect' in *qgraph*) (Epskamp et al., 2012) . The algorithm selects which edges to include in a network and estimates their weights. One hundred networks are initially estimated, ranging from very sparse (i.e., with few edges) to very dense, using the graphical least absolute shrinkage and selection

operator (gLASSO). LASSO regularisation sets an upper bound to the total sum of parameters in the network, with the aim of minimising the number of spurious edges (for more details, see Epskamp et al., 2012). A set of edges to include is thus obtained for each of the 100 networks. Models are subsequently re-fit without regularisation to compute the weights of included edges. The network with the optimal model is chosen by minimising the Extended Bayesian Information Criterion (EBIC). In a final step, individual edges are progressively added or removed to further improve fit (stepwise estimation).

Supplementary Results

All PGSs network

The inclusion of all PGSs simultaneously in one network did not fundamentally change results (Appendix A, Supplementary Figure 3b). Exceptions were the edges connecting the BMI PGS to items '*Does not think things out*' (HYP.4) and '*Steals'* (COND.5), the anxiety PGS to item *'Feeling lonely'* (DEP.10), and the depression PGS to item '*Not enjoying anything'* (DEP.2). An additional edge between the PGS for depression and item '*Child has many worries*' (EMO.2) was observed. Results indicated that network structure and weights were successfully replicated. Network structures had good model fit in the secondary sample (model 1; CFI ≥ 0.98, RMSEA ≤ 0.019). Constraining edges to be equal between cohorts resulted in good model fit (model 2, Appendix A, Supplementary Table 3), and this was the best fitting and most parsimonious model according to the BIC (Appendix A, Supplementary Table 3).

Additionally, all associations between PGSs and scale items were statistically significant and of similar magnitude in both cohorts. Models including edges connecting PGSs (models 3 and 4) were preferred to those excluding them. All edges connecting PGS were of similar magnitude in TEDS and ALSPAC (model 5), with the exception of the edge between the PGS for EA and item '*Child cheats*' (COND.4). However, this difference did not survive corrections for multiple comparisons.

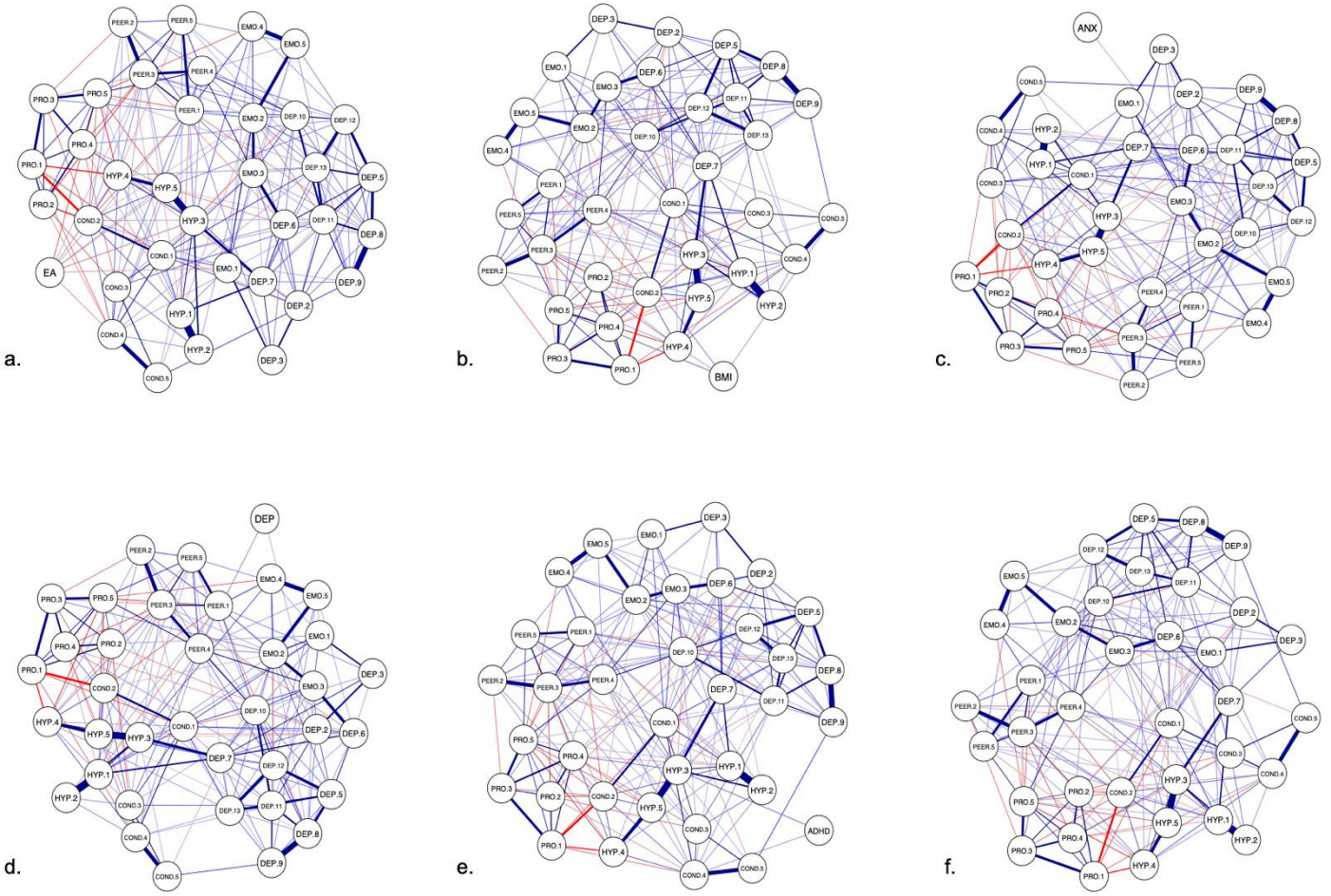
Phenotypic network

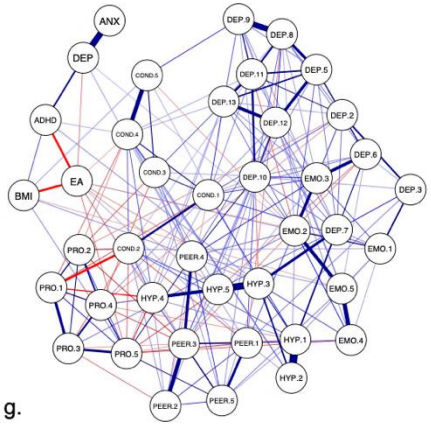
Behavioural and emotional symptoms of psychopathology were frequently positively correlated (Appendix A, Supplementary Figure 3a), not only within individual subscales (e.g., correlations among 'Peer problems' items), but also between scales (e.g., between 'Peer problems' and 'Depression' items). Overall, non-zero network edges varied in weight. The strongest positive partial correlation between phenotypic items was between node *'Overactive'* (HYP.1) and *'Fidgeting'* (HYP.2), r=0.46, while the strongest negative partial correlation was between node *'Considerate of others'* (PRO.1) and *'Disobedient'* (COND.2), r=-0.17. Results indicated the phenotypic network model was successfully replicated in the secondary sample, with similar associations between scale items in both samples. The structure of this network showed good model fit when tested in the secondary sample (model 1, CFI≥0.98, RMSEA≤0.021), based on standard fit indices thresholds. Constraining edges to be equal across cohorts resulted in good model fit (model 2, Appendix A, Supplementary Table 3), and the model where edges were constrained to be equal between cohorts was the best fitting and most parsimonious according to the BIC.

Supplementary Discussion

I note additional limitations of the study. PGSs are themselves sum-scores, and therefore, not unlike sum-scores on psychopathology scales, they might hide the complexity of the genetic architecture of disorders (e.g. interactions). Moreover, findings are dependent on PGSs derived from disorder-level GWASs. Future efforts may benefit from considering symptom-level approaches to phenotyping, such as symptom-level GWASs and network modelling.

Supplementary Figures





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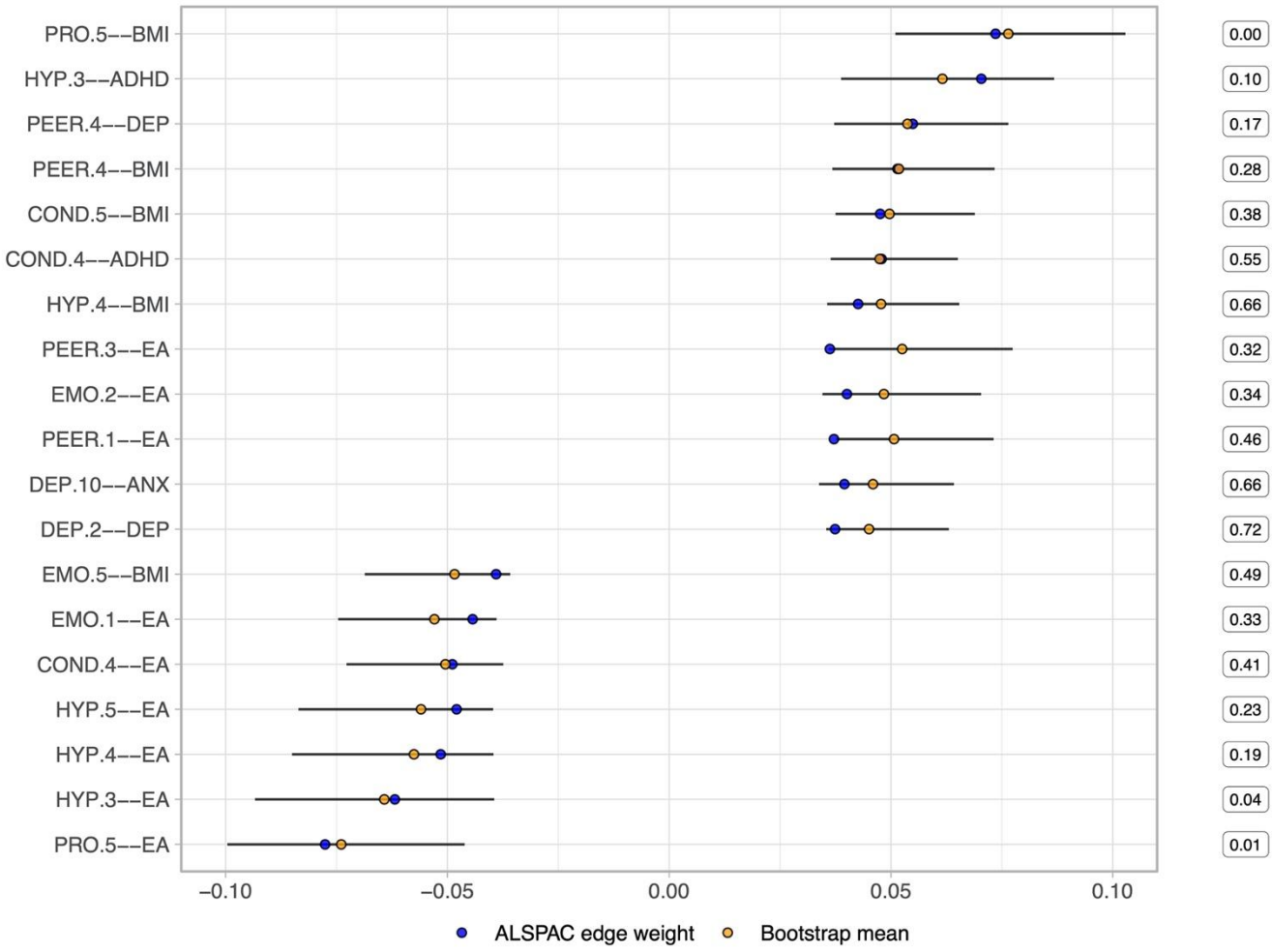
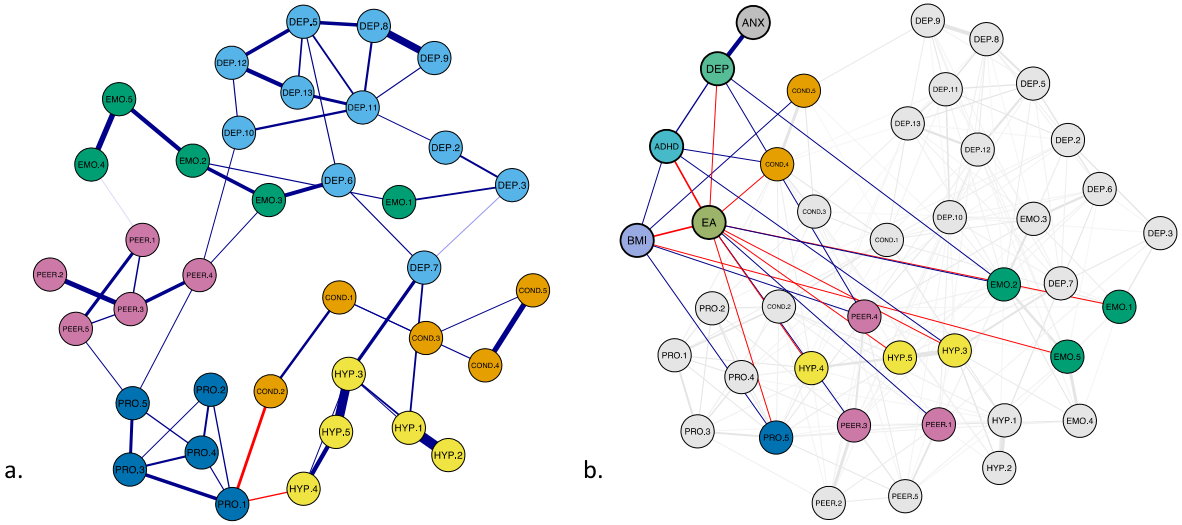
Supplementary Figure 1 (a-g): Networks of PGSs and psychopathology symptoms without formatting to highlight PGSs.

Plots for networks with the polygenic score for EA (a), BMI (b), anxiety (c), depression (d), ADHD (e), phenotypic network (f) and all PGSs (g). Positive correlations are in blue and negative in red. Please refer to Table 2.1 for node abbreviations.



Supplementary Figure 2: Weights (partial correlations) of edges connecting PGS nodes in their respective networks.

Weights were derived from primary networks (ALSPAC edge weights, in blue). Mean bootstrap edge weights (in orange) and their quantile ranges (black lines) were derived from 1000 non-parametric bootstraps. Boxes on the right indicate the proportion of times edges were not included in bootstrap networks. Please refer to Table 2.1 for node abbreviations.



Conduct Problems
- COND.1: Temper tantrums
- COND.2: Disobedient
- COND.3: Often fights
- **COND.4: Cheats**
- **COND.5: Steals**

Peer Problems
- **PEER.1: Solitary**
- PEER.2: Does not have a good friend
- **PEER.3: Not generally liked**
- **PEER.4: Bullied**
- PEER.5: Gets on better with adults

Depression
- DEP.2: Not enjoying anything
- DEP.3: Tired
- DEP.5: Felt no good
- DEP.6: Cried a lot
- DEP.7: Hard to concentrate
- DEP.8: Hated themselves
- DEP.9: Felt like a bad person
- DEP.10: Felt lonely
- DEP.11: Felt unloved
- DEP.12: Felt not as good as others
- DEP.13: Felt they did everything wrong

Emotional Problems
- **EMO.1: Complained of sickness**
- **EMO.2: Many worries**
- EMO.3: Often unhappy
- EMO.4: Nervous in new situations
- **EMO.5: Many fears**

Hyperactivity
- HYP.1: Overactive
- HYP.2: Fidgeting
- **HYP.3: Easily distracted**
- **HYP.4: Does not think things out**
- **HYP.5: Bad attention**

Prosocial Scale
- PRO.1: Considerate of others
- PRO.2: Shared readily with others
- PRO.3: Helpful
- PRO.4: Kind to younger children
- **PRO.5: Volunteers to help**

Polygenic scores
- EA: PGS for educational attainment
- BMI: PGS for BMI
- DEP: PGS for depression
- ADHD: PGS for ADHD
- ANX: PGS for anxiety

Supplementary Figure 3 (a-b): Plot of phenotypic network (a) and all PGSs network (b).

In **(a)**, partial correlations between scale items are drawn when |r| > 0.1 for clarity (threshold for *qgraph* visualization = 0.1). All edges are blue when positive and red when negative. In **(b)**, all partial correlations are drawn (*qgraph* visualization threshold = 0). Edges connecting scale items are solid grey when positive and dotted grey when negative. Bold items in the legend indicate nodes connected to a PGS.

Supplementary Tables

Supplementary Table 1: Items of the SDQ and SMFQ, with node abbreviations, endorsement frequencies, sample size (of genotyped individuals), mean and standard deviations.

Network node	Scale	Item	ALSPAC					TEDS				
			Not true	Sometimes	TRUE	Mean	SD	Not true	Sometimes	TRUE	Mean	SD
COND.1	SDQ	Temper tantrums	3332	1682	476	0.48	0.65	2457	1584	574	0.592	0.7
COND.2	SDQ	Disobedient	3326	1994	180	0.428	0.557	3040	1392	185	0.382	0.562
COND.3	SDQ	Often fights	5140	278	32	0.063	0.266	4392	195	30	0.055	0.255
COND.4	SDQ	Cheats	4539	813	73	0.177	0.415	3678	836	107	0.227	0.471
COND.5	SDQ	Steals	5324	100	17	0.025	0.174	4456	130	36	0.044	0.24
EMO.1	SDQ	Complained of sickness	3519	1630	331	0.418	0.603	3206	1118	288	0.367	0.598
EMO.2	SDQ	Many worries	3878	1373	196	0.324	0.539	2961	1328	325	0.429	0.621
EMO.3	SDQ	Often unhappy	4636	763	88	0.171	0.417	3814	673	128	0.201	0.465
EMO.4	SDQ	Nervous in new situations	4077	1196	215	0.296	0.536	2842	1446	330	0.456	0.625
EMO.5	SDQ	Many fears	4428	913	115	0.209	0.456	3384	1012	221	0.315	0.558
HYP.1	SDQ	Overactive, Restless	4030	1130	298	0.316	0.571	3120	1122	374	0.405	0.635
HYP.2	SDQ	Fidgeting	4279	928	269	0.268	0.543	3450	867	300	0.318	0.589
HYP.3	SDQ	Easily distracted	2961	1917	613	0.572	0.684	2579	1613	422	0.533	0.657
HYP.4	SDQ	Does not think things out	1349	3431	611	0.863	0.587	1244	2807	555	0.85	0.607
HYP.5	SDQ	Bad attention	2250	2553	677	0.713	0.672	2011	2074	532	0.68	0.67
PEER.1	SDQ	Solitary	4157	1136	184	0.275	0.516	3612	830	180	0.257	0.519
PEER.2	SDQ	Does not have a good friend	4811	540	127	0.145	0.413	3991	530	97	0.157	0.417
PEER.3	SDQ	Not generally liked	4543	881	55	0.181	0.41	3907	640	66	0.167	0.41
PEER.4	SDQ	Bullied	4218	955	154	0.237	0.489	3636	793	185	0.252	0.518

PEER.5	SDQ	Gets on better with adults	4295	902	151	0.225	0.481	3700	755	161	0.233	0.499
PRO.1	SDQ	Considerate of others	80	2021	3382	1.602	0.518	76	1339	3207	1.677	0.501
PRO.2	SDQ	Shared readily with others	98	1324	4044	1.722	0.486	171	1117	3304	1.682	0.54
PRO.3	SDQ	Helpful	86	1194	4210	1.751	0.467	86	845	3691	1.78	0.457
PRO.4	SDQ	Kind to younger children	23	801	4663	1.846	0.373	67	502	4052	1.862	0.384
PRO.5	SDQ	Volunteers to help	366	2301	2726	1.438	0.618	249	1546	2823	1.557	0.596
DEP.10	SMFQ	Felt lonely	4742	700	64	0.15	0.389	4178	386	52	0.106	0.343
DEP.11	SMFQ	Felt unloved	4979	477	45	0.103	0.33	4312	269	33	0.073	0.286
DEP.12	SMFQ	Felt not as good as others	4868	565	69	0.128	0.37	3956	590	72	0.159	0.406
DEP.13	SMFQ	Felt they did everything wrong	4539	891	74	0.189	0.424	4042	519	55	0.136	0.376
DEP.2	SMFQ	Not enjoying anything	4778	653	61	0.141	0.379	4362	216	43	0.065	0.282
DEP.3	SMFQ	Tired	4264	1153	93	0.243	0.467	4122	443	51	0.118	0.355
DEP.5	SMFQ	Felt no good	4874	564	63	0.125	0.364	4214	354	46	0.097	0.328
DEP.6	SMFQ	Cried a lot	4922	521	61	0.117	0.354	4267	301	45	0.085	0.312
DEP.7	SMFQ	Hard to concentrate	4476	917	112	0.207	0.453	3879	683	58	0.173	0.41
DEP.8	SMFQ	Hated themselves	5146	324	38	0.073	0.285	4346	226	46	0.069	0.29
DEP.9	SMFQ	Felt like a bad person	5220	262	25	0.057	0.25	4424	176	18	0.046	0.227

Supplementary Table 2: Number of SNPs resulting from GWAS QC procedures and SNPs included in polygenic scores (PGSs).

GWAS	Trait	Sample size	Sample ancestry	SNP-heritability	SNPs pre-QC	Non autosomal SNPs	Info < 0.8	MAF < 0.1	Ambiguous SNPs	Duplicate SNPs	QC-positive SNPs ALSPAC	SNPs included in PGSs overlapping with ALSPAC	QC-positive SNPs TEDS	SNPs included in PGSs overlapping with TEDS
Yengo et al., 2018	BMI	456,426	European	0.06	2336269	0	0	0	358380	7	1977882	519336	922666	868323
Lee et al., 2018	EA	1,131,881	European	0.3	10101242	0	0	0	1503339	0	8597903	575161	1362676	1211019
Demontis et al., 2019	ADHD	20,183 cases, 35,191 controls	European, North American, Chinese	0.216	8047420	0	0	0	1121345	0	6926075	552661	1145060	1069012
Purves et al., 2020	Anxiety	31,977 cases and 82,114 controls	European	0.26	7926782	0	170	0	1213020	57577	6656015	595918	934238	867312
Howard et al., 2019	Depression	246,363 cases and 561,190 controls	European	0.089	8483301	0	0	0	1297781	0	7185520	570459	1029373	965349

Supplementary Table 3: Model fit indices for Model 2 in all networks and model comparisons between constrained and unconstrained models in all networks.

Fit index	Phenotypic network	ADHD PGS network	Depression PGS network	Anxiety PGS network	EA PGS network	BMI PGS network	All PGS network	
cfi	0.978	0.977	0.978	0.978	0.977	0.977	0.977	
rmsea	0.02	0.02	0.019	0.019	0.019	0.02	0.018	
model	**DF**	**AIC**	**BIC**	**RMSEA**	**Chisq**	**Chisq_diff**	**DF_diff**	**p_value**
Phenotypic network								
not constrained	850	943240	947242.5	0.017	2075.527			
constrained	1055	943884	946405.5	0.02	3129.6	1054.073	205	< 0.0001
All PGS network								
not constrained	1196	1083556	1087949	0.015	2640.415			
constrained	1418	1084189	1086978	0.018	3717.176	1076.762	222	< 0.0001
BMI PGS network								
not constrained	916	971943.2	976018	0.017	2242.29			
constrained	1124	972585	975157.1	0.02	3300.152	1057.863	208	< 0.0001
Depression PGS network								
not constrained	918	971973.3	976033.7	0.016	2141.459			
constrained	1125	972627.7	975192.5	0.019	3209.808	1068.349	207	< 0.0001
ADHD PGS network								

not constrained	920	971926.3	975972.2	0.017	2245.815			
constrained	1126	972567.4	975125	0.02	3298.985	1053.17	206	< 0.0001
EA PGS network								
not constrained	904	971651.9	975813.4	0.017	2189.186			
constrained	1118	972308.5	974923.9	0.019	3273.819	1084.633	214	< 0.0001
ANX PGS network								
not constrained	922	972055.8	976087.3	0.017	2196.555			
constrained	1127	972704	975254.4	0.019	3254.764	1058.209	205	< 0.0001

RMSEA: Root Mean Square Error of Approximation; CFI: Comparative Fit Index.DF: Degrees of Freedom; AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; Chisq: Chi Square; Chisq_diff: Chi Square difference; DF_diff: Degrees of Freedom difference

Supplementary Table 4: Model 3 results: model comparisons between models with all PGS edges, and models without PGS edges in each network.

model	DF	AIC	BIC	RMSEA	Chisq	Chisq_diff	DF_diff	p_value
All PGS network								
all pgs original	1418	1084189	1086978	0.018	3717.176			
allpgs no pgs edges	1441	1087953	1090575	0.029	7526.953	3809.776	23	< 0.0001
BMI PGS network								
bmi original	1124	972585	975157.1	0.02	3300.152			
bmi no pgs	1129	972728.8	975264.8	0.02	3453.975	153.823	5	< 0.0001
Depression PGS network								
dep original	1125	972627.7	975192.5	0.019	3209.808			
dep no pgs	1127	972680.5	975230.8	0.019	3266.597	56.788	2	< 0.0001
ADHD PGS network								
adhd original	1126	972567.4	975125	0.02	3298.985			
adhd no pgs	1128	972701.9	975245	0.02	3437.405	138.42	2	< 0.0001
ANX PGS network								
anx original	1127	972704	975254.4	0.019	3254.764			
anx no pgs	1128	972714.9	975258	0.019	3267.607	12.843	1	< 0.0001
EA PGS network								
ea original	1118	972308.49	974923.88	0.019	3273.82			
ea no pgs	1127	972688.01	975238.38	0.021	3671.34	397.52	9	< 0.0001

RMSEA: Root Mean Square Error of Approximation; CFI: Comparative Fit Index.DF: Degrees of Freedom; AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; Chisq: Chi Square; Chisq_diff: Chi Square difference; DF_diff: Degrees of Freedom difference

Supplementary Table 5: Model 4 results: model comparisons between models with all PGSs edges (original), and models without a single PRS edge in each network.

model	DF	AIC	BIC	RMSEA	Chisq	Chisq_diff	DF_diff	p_value	FDR_corrected_pvalue (34 tests)
All PGS network									
all pgs original	**1418**	**1084189**	**1086978**	**0.018**	**3717.176**				
all pgs no bmi-peer4	**1419**	**1084223**	**1087004**	**0.018**	**3753.259**	**36.083**	**1**	**< 0.0001**	**< 0.0001**
all pgs original	**1418**	**1084189**	**1086978**	**0.018**	**3717.176**				
all pgs no bmi-pro5	**1419**	**1084229**	**1087010**	**0.018**	**3758.981**	**41.805**	**1**	**< 0.0001**	**< 0.0001**
all pgs original	**1418**	**1084189**	**1086978**	**0.018**	**3717.176**				
all pgs no bmi-cond5	**1419**	**1084204**	**1086985**	**0.018**	**3734.287**	**17.11**	**1**	**< 0.0001**	**0.0001**
all pgs original	**1418**	**1084189**	**1086978**	**0.018**	**3717.176**				
all pgs no bmi-emo5	**1419**	**1084194**	**1086976**	**0.018**	**3724.661**	**7.484**	**1**	**0.006**	**0.0064**
all pgs original	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**				
all pgs no ea-emo1	**1,419**	**1,084,197**	**1,086,978**	**0.018**	**3,727.27**	**10.093**	**1**	**0.001**	**0.0017**
all pgs original	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**				
all pgs no ea-peer1	**1,419**	**1,084,194**	**1,086,976**	**0.018**	**3,724.82**	**7.647**	**1**	**0.006**	**0.0060**
all pgs original	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**				
all pgs no ea-emo2	**1,419**	**1,084,223**	**1,087,004**	**0.018**	**3,753.28**	**36.105**	**1**	**< 0.0001**	**< 0.0001**

all pgs original	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**				
all pgs no ea-peer3	**1,419**	**1,084,204**	**1,086,985**	**0.018**	**3,734.12**	**16.946**	**1**	**< 0.0001**	**0.0001**
all pgs original	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**				
all pgs no ea-hyp3	**1,419**	**1,084,207**	**1,086,988**	**0.018**	**3,737.12**	**19.942**	**1**	**< 0.0001**	**< 0.0001**
all pgs original	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**				
all pgs no ea-cond4	**1,419**	**1,084,234**	**1,087,015**	**0.018**	**3,764.25**	**47.069**	**1**	**< 0.0001**	**< 0.0001**
all pgs original	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**				
all pgs no ea-pro5	**1,419**	**1,084,229**	**1,087,010**	**0.018**	**3,759.22**	**42.044**	**1**	**< 0.0001**	**< 0.0001**
all pgs original	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**				
all pgs no ea-hyp4	**1,419**	**1,084,204**	**1,086,985**	**0.018**	**3,734.10**	**16.924**	**1**	**< 0.0001**	**0.0001**
all pgs original	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**				
all pgs no ea-hyp5	**1,419**	**1,084,222**	**1,087,004**	**0.018**	**3,752.32**	**35.145**	**1**	**< 0.0001**	**< 0.0001**
all pgs original	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**				
all pgs no dep-peer4	**1,419**	**1,084,203**	**1,086,984**	**0.018**	**3,733.32**	**16.14**	**1**	**< 0.0001**	**0.0001**
all pgs original	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**				

all pgs no dep-emo2	**1,419**	**1,084,207**	**1,086,988**	**0.018**	**3,736.97**	**19.788**	**1**	**< 0.0001**	**< 0.0001**
all pgs original	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**				
all pgs no adhd-cond4	**1,419**	**1,084,197**	**1,086,979**	**0.018**	**3,727.84**	**10.668**	**1**	**0.001**	**0.0013**
all pgs original	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**				
all pgs no adhd-hyp3	**1,419**	**1,084,236**	**1,087,018**	**0.018**	**3,766.84**	**49.663**	**1**	**< 0.0001**	**< 0.0001**
BMI PGS network									
original bmi	**1,124**	**972,585.00**	**975,157.10**	**0.02**	**3,300.15**				
no edge bmi-peer	**1,125**	**972,618.40**	**975,183.20**	**0.02**	**3,335.57**	**35.413**	**1**	**< 0.0001**	**< 0.0001**
original bmi	**1,124**	**972,585.00**	**975,157.10**	**0.02**	**3,300.15**				
no edge bmi-pro	**1,125**	**972,649.10**	**975,213.90**	**0.02**	**3,366.20**	**66.05**	**1**	**< 0.0001**	**< 0.0001**
original bmi	**1,124**	**972,585.00**	**975,157.10**	**0.02**	**3,300.15**				
no edge bmi-hyp	**1,125**	**972,604.70**	**975,169.50**	**0.02**	**3,321.80**	**21.645**	**1**	**< 0.0001**	**< 0.0001**
original bmi	**1,124**	**972,585.00**	**975,157.10**	**0.02**	**3,300.15**				
no edge bmi-cond	**1,125**	**972,605.30**	**975,170.20**	**0.02**	**3,322.47**	**22.322**	**1**	**< 0.0001**	**< 0.0001**
original bmi	**1,124**	**972,585**	**975,157.10**	**0.02**	**3,300.15**				

no edge bmi-emo	**1,125**	**972,592**	**975,156.80**	**0.02**	**3,309.12**	**8.971**	**1**	**0.003**	**0.0030**
Depression PGS network									
original dep	**1,125**	**972,627.70**	**975,192.50**	**0.019**	**3,209.81**				
no edge dep-peer	**1,126**	**972,654.50**	**975,212.10**	**0.019**	**3,238.66**	**28.85**	**1**	**< 0.0001**	**< 0.0001**
original dep	**1,125**	**972,627.70**	**975,192.50**	**0.019**	**3,209.81**				
no edge dep-dep2	**1,126**	**972,644.30**	**975,201.90**	**0.019**	**3,228.41**	**18.605**	**1**	**< 0.0001**	**< 0.0001**
ADHD PGS network									
adhd original	**1,126**	**972,567.40**	**975,125.00**	**0.02**	**3,298.99**				
no edge adhd-hyp	**1,127**	**972,650.60**	**975,200.90**	**0.02**	**3,384.13**	**85.14**	**1**	**< 0.0001**	**< 0.0001**
adhd original	**1,126**	**972,567.40**	**975,125**	**0.02**	**3,298.99**				
no edge adhd-cond	**1,127**	**972,591.60**	**975,142**	**0.02**	**3,325.17**	**26.184**	**1**	**< 0.0001**	**< 0.0001**
EA PGS network									
original ea	**1,118**	**972,308.50**	**974,923.90**	**0.019**	**3,273.82**				
no edge ea-emo1	**1,119**	**972,316.70**	**974,924.90**	**0.02**	**3,284.08**	**10.262**	**1**	**0.001**	**0.0016**
original ea	**1,118**	**972,308.50**	**974,923.90**	**0.019**	**3,273.82**				
no edge ea-emo2	**1,119**	**972,336.00**	**974,944.20**	**0.02**	**3,303.32**	**29.504**	**1**	**< 0.0001**	**< 0.0001**

original ea	**1,118**	**972,308.50**	**974,923.90**	**0.019**	**3,273.82**				
no edge ea-hyp3	**1,119**	**972,341.70**	**974,949.90**	**0.02**	**3,309.05**	**35.23**	**1**	**< 0.0001**	**< 0.0001**
original ea	**1,118**	**972,308.50**	**974,923.90**	**0.019**	**3,273.82**				
no edge ea-hyp4	**1,119**	**972,323.50**	**974,931.60**	**0.02**	**3,290.79**	**16.974**	**1**	**< 0.0001**	**0.0001**
original ea	**1,118**	**972,308.50**	**974,923.90**	**0.019**	**3,273.82**				
no edge ea-hyp5	**1,119**	**972,341.70**	**974,949.90**	**0.02**	**3,309.02**	**35.202**	**1**	**< 0.0001**	**< 0.0001**
original ea	**1,118**	**972,308.50**	**974,923.90**	**0.019**	**3,273.82**				
no edge ea-peer1	**1,119**	**972,313.50**	**974,921.70**	**0.02**	**3,280.87**	**7.054**	**1**	**0.008**	**0.0079**
original ea	**1,118**	**972,308.50**	**974,923.90**	**0.019**	**3,273.82**				
no edge ea-cond4	**1,119**	**972,372.00**	**974,980.20**	**0.02**	**3,339.37**	**65.552**	**1**	**< 0.0001**	**< 0.0001**
original ea	**1,118**	**972,308.50**	**974,923.90**	**0.019**	**3,273.82**				
no edge ea-pro5	**1,119**	**972,372.70**	**974,980.80**	**0.02**	**3,340.00**	**66.183**	**1**	**< 0.0001**	**< 0.0001**

RMSEA: Root Mean Square Error of Approximation; CFI: Comparative Fit Index.DF: Degrees of Freedom; AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; Chisq: Chi Square; Chisq_diff: Chi Square difference; DF_diff: Degrees of Freedom difference; FDR: False Discovery Rate.

Supplementary Table 6: Model 5 results: model comparisons between models where PRS edges are equal between ALSPAC and TEDS (original) and models where they are free to vary.

model	DF	AIC	BIC	RMSEA	Chisq	Chisq_diff	DF_diff	p_value	FDR_corrected_pvalue (35 tests)
All PGS network									
free adhd-cond4	**1,417**	**1,084,190**	**1,086,986**	**0.018**	**3,716.81**				
original allpgs	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**	**0.369**	**1**	**0.544**	**0.906**
free adhd-hyp3	**1,417**	**1,084,191**	**1,086,987**	**0.018**	**3,717.02**				
original allpgs	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**	**0.161**	**1**	**0.688**	**0.944**
free dep-peer4	**1,417**	**1,084,189**	**1,086,985**	**0.018**	**3,715.08**				
original allpgs	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**	**2.095**	**1**	**0.148**	**0.470**
free dep-emo2	**1,417**	**1,084,191**	**1,086,987**	**0.018**	**3,717.14**				
original allpgs	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**	**0.039**	**1**	**0.843**	**0.944**

free ea-emo1	**1,417**	**1,084,188**	**1,086,984**	**0.018**	**3,713.94**				
original allpgs	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**	**3.238**	**1**	**0.072**	**0.420**
free ea-peer1	**1,417**	**1,084,188**	**1,086,984**	**0.018**	**3,713.89**				
original allpgs	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**	**3.291**	**1**	**0.07**	**0.420**
free ea-emo2	**1,417**	**1,084,190**	**1,086,986**	**0.018**	**3,716.69**				
original allpgs	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**	**0.491**	**1**	**0.484**	**0.906**
free ea-peer3	**1,417**	**1,084,190**	**1,086,986**	**0.018**	**3,716.51**				
original allpgs	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**	**0.669**	**1**	**0.413**	**0.904**
free ea-hyp3	**1,417**	**1,084,190**	**1,086,986**	**0.018**	**3,716.31**				

original allpgs	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**	**0.864**	**1**	**0.353**	**0.823**
free ea-cond4	**1,417**	**1,084,186**	**1,086,982**	**0.018**	**3,712.37**				
original allpgs	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**	**4.807**	**1**	**0.028**	**0.420**
free ea-pro5	**1,417**	**1,084,191**	**1,086,987**	**0.018**	**3,717.14**				
original allpgs	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**	**0.038**	**1**	**0.846**	**0.944**
free ea-hyp4	**1,417**	**1,084,189**	**1,086,985**	**0.018**	**3,715.85**				
original allpgs	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**	**1.326**	**1**	**0.25**	**0.672**
free ea-hyp5	**1,417**	**1,084,191**	**1,086,987**	**0.018**	**3,717.14**				
original allpgs	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**	**0.035**	**1**	**0.851**	**0.944**

free bmi-peer4	**1,417**	**1,084,191**	**1,086,987**	**0.018**	**3,717.14**				
original allpgs	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**	**0.032**	**1**	**0.857**	**0.944**
free bmi-pro5	**1,417**	**1,084,191**	**1,086,987**	**0.018**	**3,717.18**				
original allpgs	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**	**0.002**	**1**	**0.967**	**0.973**
free bmi-cond5	**1,417**	**1,084,191**	**1,086,987**	**0.018**	**3,716.95**				
original allpgs	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**	**0.228**	**1**	**0.633**	**0.944**
free bmi-emo5	**1,417**	**1,084,188**	**1,086,984**	**0.018**	**3,714.57**				
original allpgs	**1,418**	**1,084,189**	**1,086,978**	**0.018**	**3,717.18**	**2.608**	**1**	**0.106**	**0.426**
BMI PGS network									
free bmi-hyp	**1,123**	**972,587**	**975,166.30**	**0.02**	**3,300.14**				

original bmi	**1,124**	**972,585**	**975,157.10**	**0.02**	**3,300.15**	**0.009**	**1**	**0.923**	**0.973**
free bmi-emo	**1,123**	**972,584.40**	**975,163.70**	**0.02**	**3,297.54**				
original bmi	**1,124**	**972,585.00**	**975,157.10**	**0.02**	**3,300.15**	**2.612**	**1**	**0.106**	**0.426**
free bmi-cond	**1,123**	**972,586.80**	**975,166.00**	**0.02**	**3,299.92**				
original bmi	**1,124**	**972,585.00**	**975,157.10**	**0.02**	**3,300.15**	**0.233**	**1**	**0.629**	**0.944**
free bmi-peer	**1,123**	**972,587**	**975,166.30**	**0.02**	**3,300.12**				
original bmi	**1,124**	**972,585**	**975,157.10**	**0.02**	**3,300.15**	**0.03**	**1**	**0.863**	**0.944**
free bmi-pro	**1,123**	**972,587**	**975,166.30**	**0.02**	**3,300.15**				
original bmi	**1,124**	**972,585**	**975,157.10**	**0.02**	**3,300.15**	**0.001**	**1**	**0.973**	**0.973**

Depression PGS network									
free dep-peer	**1,124**	**972,627.50**	**975,199.60**	**0.019**	**3,207.63**				
original dep	**1,125**	**972,627.70**	**975,192.50**	**0.019**	**3,209.81**	**2.178**	**1**	**0.14**	**0.470**
free dep-dep2	**1,124**	**972,629.30**	**975,201.30**	**0.019**	**3,209.38**				
original dep	**1,125**	**972,627.70**	**975,192.50**	**0.019**	**3,209.81**	**0.432**	**1**	**0.511**	**0.906**
ADHD PGS network									
free edge adhd-hyp	**1,125**	**972,569.30**	**975,134.10**	**0.02**	**3,298.82**				
adhd original	**1,126**	**972,567.40**	**975,125.00**	**0.02**	**3,298.99**	**0.165**	**1**	**0.684**	**0.944**
free edge adhd-cond	**1,125**	**972,569.10**	**975,133.90**	**0.02**	**3,298.61**				
adhd original	**1,126**	**972,567.40**	**975,125.00**	**0.02**	**3,298.99**	**0.377**	**1**	**0.539**	**0.906**
EA PGS network									
free ea-emo1	**1,117**	**972,307.20**	**974,929.80**	**0.019**	**3,270.56**				

original ea	**1,118**	**972,308.50**	**974,923.90**	**0.019**	**3,273.82**	**3.262**	**1**	**0.071**	**0.420**
free ea-emo2	**1,117**	**972,310.00**	**974,932.60**	**0.02**	**3,273.34**				
original ea	**1,118**	**972,308.50**	**974,923.90**	**0.019**	**3,273.82**	**0.479**	**1**	**0.489**	**0.906**
free ea-hyp3	**1,117**	**972,309.60**	**974,932.20**	**0.02**	**3,272.91**				
original ea	**1,118**	**972,308.50**	**974,923.90**	**0.019**	**3,273.82**	**0.911**	**1**	**0.34**	**0.823**
free ea-hyp4	**1,117**	**972,309.10**	**974,931.70**	**0.02**	**3,272.46**				
original ea	**1,118**	**972,308.50**	**974,923.90**	**0.019**	**3,273.82**	**1.363**	**1**	**0.243**	**0.672**
free ea-hyp5	**1,117**	**972,310.40**	**974,933.10**	**0.02**	**3,273.77**				
original ea	**1,118**	**972,308.50**	**974,923.90**	**0.019**	**3,273.82**	**0.045**	**1**	**0.832**	**0.944**
free ea-peer1	**1,117**	**972,307.20**	**974,929.80**	**0.019**	**3,270.51**				
original ea	**1,118**	**972,308.50**	**974,923.90**	**0.019**	**3,273.82**	**3.307**	**1**	**0.069**	**0.420**

free ea-cond4	**1,117**	**972,305.80**	**974,928.40**	**0.019**	**3,269.09**				
original ea	**1,118**	**972,308.50**	**974,923.90**	**0.019**	**3,273.82**	**4.731**	**1**	**0.03**	**0.420**
free ea-pro5	**1,117**	**972,310.40**	**974,933.10**	**0.02**	**3,273.78**				
original ea	**1,118**	**972,308.50**	**974,923.90**	**0.019**	**3,273.82**	**0.042**	**1**	**0.838**	**0.944**
ANX PGS network									
free dep-dep2	**1,126**	**972,703.50**	**975,261.10**	**0.019**	**3,252.20**				
original anx	**1,127**	**972,704.00**	**975,254.40**	**0.019**	**3,254.76**	**2.563**	**1**	**0.109**	**0.426**

RMSEA: Root Mean Square Error of Approximation; CFI: Comparative Fit Index.DF: Degrees of Freedom; AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; Chisq: Chi Square; Chisq_diff: Chi Square difference; DF_diff: Degrees of Freedom difference; FDR: False Discovery Rate.

Supplementary Table 7: BMI PGS network matrix

Node	DEP.2	DEP.3	DEP.5	DEP.6	DEP.7	DEP.8	DEP.9	DEP.10	DEP.11	DEP.12	DEP.13	PRO.1	HYP.1	EMO.1	PRO.2	COND.1	PEER.1	COND.2	EMO.2	PRO.3	HYP.2	PEER.2	COND.3	EMO.3	PEER.3	HYP.3	EMO.4	PRO.4	COND.4	PEER.4	PRO.5	HYP.4	COND.5	PEER.5	EMO.5	HYP.5	BMI
DEP.2	0	0.15	0.08	0.1	0.07	0.06	0	0	0.11	0	0.04	0	0	0	-0.05	0.08	0	0	0.05	0	0	0	0	0.07	0	0	0	-0.05	0	0	0	0	0	0	0	0	0
DEP.3	0.15	0	0	0.04	0.1	0	0	0.04	0	0	0	0	0	0.14	0	0	0.06	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
DEP.5	0.08	0	0	0.12	0.06	0.2	0.06	0.06	0.14	0.21	0.14	0	0	0	0	0	0	0	0.07	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
DEP.6	0.1	0.04	0.12	0	0.11	0.06	0	0.05	0	0	0	0	0	0	0	0.06	0	0	0	0	0	0	0	0.22	-0.04	0	0	0	0	0	0	0	0	-0.04	0.04	-0.06	0
DEP.7	0.07	0.1	0.06	0.11	0	0	0.05	0.06	0	0.07	0.06	0	0.14	0.05	0	0	0	0	0	0	0	0	0	0	0	0.2	0	0	0	0	0	0	0	0	0	0.07	0
DEP.8	0.06	0	0.2	0.06	0	0	0.35	0.07	0.15	0.1	0.04	0	0	0	0	0	-0.06	0	0.04	0	0	0	0	0.04	0	0	0	0	0	0	0	0	0	0	0	0	0
DEP.9	0	0	0.06	0	0.05	0.35	0	0.04	0.12	0.05	0.07	0	0	0	0	0.03	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.09	0	0.05	0	0
DEP.10	0	0.04	0.06	0.05	0.06	0.07	0.04	0	0.16	0.12	0	0	0	0	0	-0.04	0.08	0	0.07	0	0	0.05	0	0.09	0.08	-0.04	0	0	0	0.11	0	0	0	0.05	0	0	0
DEP.11	0.11	0	0.14	0	0	0.15	0.12	0.16	0	0	0.18	0	0	0	0	0.05	0	0.04	-0.06	0	0	0	0.07	0.05	0	-0.03	0	0	0.04	0	0.03	0	0	0	0	0	0
DEP.12	0	0	0.21	0	0.07	0.1	0.05	0.12	0	0	0.23	0	0	0	0	0	0	0	0	0	0	0	0	0	0.03	0	0.05	0.05	0	0.07	0	0	0	0	0.06	0.05	0
DEP.13	0.04	0	0.14	0	0.06	0.04	0.07	0	0.18	0.23	0	0	0	0	0	0.09	0	0	0.06	0	0	0	0	0.05	0	0	0	0	0.04	0	0	0.04	0	0.04	0	0	0
PRO.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.12	-0.08	0	-0.17	0	0.2	0	0	0	0	0	0	0	0.12	-0.07	0	0.1	-0.12	0	0	0	0	0
HYP.1	0	0	0	0	0.14	0	0	0	0	0	0	0	0	0.05	0	0.09	-0.05	0.08	0	0	0.46	0	0	0	-0.04	0.11	0	-0.04	0	0	0.04	0.05	0	0.04	0	0	0
EMO.1	0	0.14	0	0	0.05	0	0	0	0	0	0	0	0.05	0	0.04	0.09	0	0	0.11	0	0	0	0	0.08	0	0	0.04	0	0	0	0	0	0	0	0.04	0	0
PRO.2	-0.05	0	0	0	0	0	0	0	0	0	0	0.12	0	0.04	0	0	0	-0.1	0	0.11	0	0	-0.07	0	-0.09	0	0	0.14	-0.05	0	0.08	0	0	0	0	0	0
COND.1	0.08	0	0	0.06	0	0	0.03	-0.04	0.05	0	0.09	-0.08	0.09	0.09	0	0	0	0.17	0	0	0	-0.04	0.1	0.09	0	0	0	0	0.11	0	0	0.04	0	0	0	0	0
PEER.1	0	0.06	0	0	0	-0.06	0	0.08	0	0	0	0	-0.05	0	0	0	0	-0.07	0.04	0	0.04	0.09	0	0.07	0.13	0	0.1	0	0	0.04	-0.08	0	0	0.19	0	0	0
COND.2	0	0	0	0	0	0	0	0	0.04	0	0	-0.17	0.08	0	-0.1	0.17	-0.07	0	-0.03	-0.07	0	0.05	0	0	0.05	0	0	0	0.07	0	-0.07	0.08	0	0	0	0.08	0
EMO.2	0.05	0	0.07	0	0	0.04	0	0.07	-0.06	0	0.06	0	0	0.11	0	0	0.04	-0.03	0	0.06	0.05	0	0	0.21	0.04	0	0.1	0	0	0.06	0	0	-0.04	0	0.23	0	0
PRO.3	0	0	0	0	0	0	0	0	0	0	0	0.2	0	0	0.11	0	0	-0.07	0.06	0	0	-0.06	0	0	-0.04	0	0	0.15	0	0	0.18	0	0	0	0	0	0
HYP.2	0	0	0	0	0	0	0	0	0	0	0	0	0.46	0	0	0	0.04	0	0.05	0	0	0	0.07	0	0	0.14	0	0	0.05	0	0	0	0	0	0	0	0
PEER.2	0	0	0	0	0	0	0	0.05	0	0	0	0	0	0	0	-0.04	0.09	0.05	0	-0.06	0	0	0	0	0.26	0	0	0	0	0.05	0	0.05	0	0.09	0	0	0

COND.3	0	0	0	0	0	0	0	0	0.07	0	0	0	0	0	-0.07	0.1	0	0	0	0	0.07	0	0	0.04	0	0	0	-0.07	0.1	0.07	0	0	0.11	0.04	0	0	0
EMO.3	0.07	0	0	0.22	0	0.04	0	0.09	0.05	0	0.05	0	0	0.08	0	0.09	0.07	0	0.21	0	0	0	0.04	0	0	0	0	0	0	0.11	0	0	0	0	0	0	0
PEER.3	0	0	0	-0.04	0	0	0	0.08	0	0.03	0	0	-0.04	0	-0.09	0	0.13	0.05	0.04	-0.04	0	0.26	0	0	0	0	0	-0.08	0	0.2	-0.04	0.06	0	0.12	0	0.05	0
HYP.3	0	0	0	0	0.2	0	0	-0.04	-0.03	0	0	0	0.11	0	0	0	0	0	0	0	0.14	0	0	0	0	0	0.08	0.07	0	0.05	0	0.11	0.04	0.04	0	0.41	0
EMO.4	0	0	0	0	0	0	0	0	0	0.05	0	0	0	0.04	0	0	0.1	0	0.1	0	0	0	0	0	0	0.08	0	0	0	0	-0.07	0	0	0	0.28	0	0
PRO.4	-0.05	0	0	0	0	0	0	0	0	0.05	0	0.12	-0.04	0	0.14	0	0	0	0	0.15	0	0	-0.07	0	-0.08	0.07	0	0	0	0	0.12	0	0	0	0	-0.05	0
COND.4	0	0	0	0	0	0	0	0	0.04	0	0.04	-0.07	0	0	-0.05	0.11	0	0.07	0	0	0.05	0	0.1	0	0	0	0	0	0	0	0.05	0	0.08	0.27	0	0	0.05	0
PEER.4	0	0	0	0	0	0	0	0.11	0	0.07	0	0	0	0	0	0	0.04	0	0.06	0	0	0.05	0.07	0.11	0.2	0.05	0	0	0.05	0	0.11	0	0	0.09	0.05	0	0.05
PRO.5	0	0	0	0	0	0	0	0	0.03	0	0	0.1	0.04	0	0.08	0	-0.08	-0.07	0	0.18	0	0	0	0	-0.04	0	-0.07	0.12	0	0.11	0	-0.1	0	0.1	0	-0.07	0.07
HYP.4	0	0	0	0	0	0	0	0	0	0	0.04	-0.12	0.05	0	0	0.04	0	0.08	0	0	0	0.05	0	0	0.06	0.11	0	0	0.08	0	-0.1	0	0	-0.05	0	0.23	0.04
COND.5	0	0	0	0	0	0	0.09	0	0	0	0	0	0	0	0	0	0	0	-0.04	0	0	0	0.11	0	0	0.04	0	0	0.27	0	0	0	0	0	0	0	0.05
PEER.5	0	0	0	-0.04	0	0	0	0.05	0	0	0.04	0	0.04	0	0	0	0.19	0	0	0	0	0.09	0.04	0	0.12	0.04	0	0	0	0.09	0.1	-0.05	0	0	0.06	0	0
EMO.5	0	0	0	0.04	0	0	0.05	0	0	0.06	0	0	0	0.04	0	0	0	0	0.23	0	0	0	0	0	0	0	0.28	0	0	0.05	0	0	0	0.06	0	0	-0.04
HYP.5	0	0	0	-0.06	0.07	0	0	0	0	0.05	0	0	0	0	0	0	0	0.08	0	0	0	0	0	0	0.05	0.41	0	-0.05	0.05	0	-0.07	0.23	0	0	0	0	0
BMI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.05	0.07	0.04	0.05	0	-0.04	0	0

Supplementary Table 8: Depression PGS network matrix

Node	DEP.2	DEP.3	DEP.5	DEP.6	DEP.7	DEP.8	DEP.9	DEP.10	DEP.11	DEP.12	DEP.13	PRO.1	HYP.1	EMO.1	PRO.2	COND.1	PEER.1	COND.2	EMO.2	PRO.3	HYP.2	PEER.2	COND.3	EMO.3	PEER.3	HYP.3	EMO.4	PRO.4	COND.4	PEER.4	PRO.5	HYP.4	COND.5	PEER.5	EMO.5	HYP.5	DEP
DEP.2	0	0.15	0.08	0.09	0.07	0.06	0	0	0.1	0	0.04	0	0	0	-0.05	0.08	0	0	0.05	0	0	0	0	0.07	0	0	0	-0.05	0	0	0	0	0	0	0	0	0.04
DEP.3	0.15	0	0	0.04	0.1	0	0	0.04	0	0	0	0	0	0.14	0	0	0.06	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
DEP.5	0.08	0	0	0.11	0.07	0.2	0.06	0.06	0.14	0.21	0.13	0	0	0	0	0	0	0	0.07	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
DEP.6	0.09	0.04	0.11	0	0.12	0.05	0	0.04	0.04	0	0	0	0	0	0	0.05	0	0	0	0	0	0	0	0.22	-0.05	-0.04	0	0	0	0	0	0	0	0	0.04	-0.04	0
DEP.7	0.07	0.1	0.07	0.12	0	0	0.06	0.07	-0.04	0.06	0.07	0	0.14	0.05	0	0	0	0	0	0	0	0	0	0	0	0.2	0	0	0	0	0	0	0	0	0	0.07	0
DEP.8	0.06	0	0.2	0.05	0	0	0.35	0.08	0.15	0.1	0.04	0	0	0	0	0	-0.06	0	0.04	0	0	0	0	0.05	0	0	0	0	0	0	0	0	0	0	0	-0.03	0
DEP.9	0	0	0.06	0	0.06	0.35	0	0	0.12	0.06	0.07	0	0	0	0	0.03	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.09	0	0.05	0	0
DEP.10	0	0.04	0.06	0.04	0.07	0.08	0	0	0.17	0.12	0	0	0	0	0	-0.04	0.08	0	0.07	0	0	0.05	0	0.1	0.08	-0.05	0	0	0	0.11	0	0	0	0.04	0	0	0
DEP.11	0.1	0	0.14	0.04	-0.04	0.15	0.12	0.17	0	0	0.18	0	0	0	0	0.04	0	0.04	-0.06	0	0	0	0.07	0.04	0	0	0	0	0.04	0	0	0	0	0	0	0	0
DEP.12	0	0	0.21	0	0.06	0.1	0.06	0.12	0	0	0.23	0	0	0	0	0	0	0	0	0	0	0	0	0	0.03	0	0.05	0.05	0	0.07	0	0	0	0	0.06	0.06	0
DEP.13	0.04	0	0.13	0	0.07	0.04	0.07	0	0.18	0.23	0	0	0	0	0	0.09	0	0	0.06	0	0	0	0	0.05	0	0	0	0	0.04	0	0.04	0.05	0	0.03	0	0	0
PRO.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.12	-0.08	0	-0.17	0	0.2	0	0	0	0	0	0	0	0.12	-0.07	0	0.1	-0.12	0	0	0	0	0
HYP.1	0	0	0	0	0.14	0	0	0	0	0	0	0	0	0.05	0	0.09	-0.05	0.08	0	0	0.46	0	0.04	0	-0.04	0.11	0	-0.04	0	0	0.03	0.05	0	0.04	0	0	0
EMO.1	0	0.14	0	0	0.05	0	0	0	0	0	0	0	0.05	0	0.04	0.09	0	0	0.11	0	0	0	0	0.08	0	0	0.04	0	0	0	0	0	0	0	0.04	0	0
PRO.2	-0.05	0	0	0	0	0	0	0	0	0	0	0.12	0	0.04	0	0	0	-0.1	0	0.11	0	0	-0.07	0	-0.09	0	0	0.14	-0.05	0	0.08	0	0	0	0	0	0
COND.1	0.08	0	0	0.05	0	0	0.03	-0.04	0.04	0	0.09	-0.08	0.09	0.09	0	0	0	0.17	0	0	0	-0.04	0.1	0.09	0	0	0	0	0.11	0	0	0.04	0	0	0	0	0
PEER.1	0	0.06	0	0	0	-0.06	0	0.08	0	0	0	0	-0.05	0	0	0	0	-0.07	0.04	0	0.04	0.09	0	0.07	0.13	0	0.1	0	0	0.04	-0.08	0	0	0.19	0	0	0
COND.2	0	0	0	0	0	0	0	0	0.04	0	0	-0.17	0.08	0	-0.1	0.17	-0.07	0	-0.03	-0.07	0	0.05	0	0	0.04	0	0	0	0.07	0	-0.07	0.08	0	0	0	0.08	0
EMO.2	0.05	0	0.07	0	0	0.04	0	0.07	-0.06	0	0.06	0	0	0.11	0	0	0.04	-0.03	0	0.06	0.05	0	0	0.21	0.04	0	0.1	0	0	0.06	0	0	-0.04	0	0.24	0	0
PRO.3	0	0	0	0	0	0	0	0	0	0	0	0.2	0	0	0.11	0	0	-0.07	0.06	0	0	-0.06	0	0	-0.04	0	0	0.15	0	0	0.18	0	0	0	0	0	0
HYP.2	0	0	0	0	0	0	0	0	0	0	0	0	0.46	0	0	0	0.04	0	0.05	0	0	0	0.05	0	0	0.14	0	0	0.05	0	0	0	0	0	0	0	0
PEER.2	0	0	0	0	0	0	0	0.05	0	0	0	0	0	0	0	-0.04	0.09	0.05	0	-0.06	0	0	0	0	0.26	0	0	0	0	0.05	0	0.05	0	0.09	0	0	0

COND.3	0	0	0	0	0	0	0	0	0.07	0	0	0	0.04	0	-0.07	0.1	0	0	0	0	0.05	0	0	0.04	0.04	0	0	-0.06	0.09	0.07	0	0	0.11	0	0	0	0
EMO.3	0.07	0	0	0.22	0	0.05	0	0.1	0.04	0	0.05	0	0	0.08	0	0.09	0.07	0	0.21	0	0	0	0.04	0	0	0	0	0	0	0.11	0	0	0	0	0	0	0
PEER.3	0	0	0	-0.05	0	0	0	0.08	0	0.03	0	0	-0.04	0	-0.09	0	0.13	0.04	0.04	-0.04	0	0.26	0.04	0	0	0	0	-0.08	0	0.2	-0.04	0.06	0	0.12	0	0.05	0
HYP.3	0	0	0	-0.04	0.2	0	0	-0.05	0	0	0	0	0.11	0	0	0	0	0	0	0	0.14	0	0	0	0	0	0.08	0.07	0	0.05	0	0.11	0.04	0.04	0	0.41	0
EMO.4	0	0	0	0	0	0	0	0	0	0.05	0	0	0	0.04	0	0	0.1	0	0.1	0	0	0	0	0	0	0.08	0	0	0	0	-0.07	0	0	0	0.28	0	0
PRO.4	-0.05	0	0	0	0	0	0	0	0	0.05	0	0.12	-0.04	0	0.14	0	0	0	0	0.15	0	0	-0.06	0	-0.08	0.07	0	0	0	0	0.12	0	0	0	0	-0.05	0
COND.4	0	0	0	0	0	0	0	0	0.04	0	0.04	-0.07	0	0	-0.05	0.11	0	0.07	0	0	0.05	0	0.09	0	0	0	0	0	0	0	0.05	0	0.08	0.27	0	0	0.05	0
PEER.4	0	0	0	0	0	0	0	0.11	0	0.07	0	0	0	0	0	0	0.04	0	0.06	0	0	0.05	0.07	0.11	0.2	0.05	0	0	0.05	0	0.11	0	0	0.1	0.05	0	0.05
PRO.5	0	0	0	0	0	0	0	0	0	0	0.04	0.1	0.03	0	0.08	0	-0.08	-0.07	0	0.18	0	0	0	0	-0.04	0	-0.07	0.12	0	0.11	0	-0.1	0	0.1	0	-0.07	0
HYP.4	0	0	0	0	0	0	0	0	0	0	0.05	-0.12	0.05	0	0	0.04	0	0.08	0	0	0	0.05	0	0	0.06	0.11	0	0	0.08	0	-0.1	0	0	-0.04	0	0.24	0
COND.5	0	0	0	0	0	0	0.09	0	0	0	0	0	0	0	0	0	0	0	0	-0.04	0	0	0	0.11	0	0	0.04	0	0	0.27	0	0	0	0	0	0	0	0
PEER.5	0	0	0	0	0	0	0	0.04	0	0	0.03	0	0.04	0	0	0	0.19	0	0	0	0	0.09	0	0	0.12	0.04	0	0	0	0.1	0.1	-0.04	0	0	0.06	0	0
EMO.5	0	0	0	0.04	0	0	0.05	0	0	0.06	0	0	0	0.04	0	0	0	0	0.24	0	0	0	0	0	0	0	0.28	0	0	0.05	0	0	0	0.06	0	0	0
HYP.5	0	0	0	-0.04	0.07	-0.03	0	0	0	0.06	0	0	0	0	0	0	0	0.08	0	0	0	0	0	0	0.05	0.41	0	-0.05	0.05	0	-0.07	0.24	0	0	0	0	0
DEP	0.04	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.05	0	0	0	0	0	0	0

Supplementary Table 9: EA PGS network matrix.

Node	DEP.2	DEP.3	DEP.5	DEP.6	DEP.7	DEP.8	DEP.9	DEP.10	DEP.11	DEP.12	DEP.13	PRO.1	HYP.1	EMO.1	PRO.2	COND.1	PEER.1	COND.2	EMO.2	PRO.3	HYP.2	PEER.2	COND.3	EMO.3	PEER.3	HYP.3	EMO.4	PRO.4	COND.4	PEER.4	PRO.5	HYP.4	COND.5	PEER.5	EMO.5	HYP.5	EA
DEP.2	0	0.15	0.08	0.09	0.07	0.06	0	0	0.11	0.04	0	0	0	0	-0.05	0.08	0	0	0.05	0	0	0	0	0.07	0	0	0	-0.05	0	0	0	0	0	0	0	0	0
DEP.3	0.15	0	0	0.04	0.1	0	0	0.04	0	0	0	0	0	0.14	0	0	0.06	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
DEP.5	0.08	0	0	0.11	0.06	0.21	0.06	0.06	0.14	0.2	0.14	0	0	0	0	0	0	0	0.07	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
DEP.6	0.09	0.04	0.11	0	0.11	0.05	0	0.04	0.04	0	0	0	0	0	0	0.05	0	0	0	0	0	0	0	0.22	-0.05	0	0	0	0	0	0	0	0	0	0	-0.05	0
DEP.7	0.07	0.1	0.06	0.11	0	0	0.05	0.07	-0.04	0.06	0.07	0	0.14	0.05	0	0	0	0	0.03	0	0	0	0	0	0	0.19	0	0	0	0	0	0	0	0	0	0.08	0
DEP.8	0.06	0	0.21	0.05	0	0	0.35	0.07	0.15	0.09	0.05	0	0	0	0	0	-0.06	0	0.04	0	0	0	0	0.04	0	0	0	0	0	0	0	0	0	0	0	-0.03	0
DEP.9	0	0	0.06	0	0.05	0.35	0	0.04	0.12	0.05	0.07	0	0	0	0	0.03	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.09	0	0.05	0	0
DEP.10	0	0.04	0.06	0.04	0.07	0.07	0.04	0	0.16	0.11	0	0	0	0	0	-0.04	0.08	0	0.06	0	0	0.05	0	0.09	0.08	-0.05	0	0	0	0.11	0	0	0	0.04	0	0	0
DEP.11	0.11	0	0.14	0.04	-0.04	0.15	0.12	0.16	0	0	0.18	0	0	0	0	0.04	0	0.04	-0.06	0	0	0	0.07	0.04	0	0	0	0	0.04	0	0	0	0	0	0	0	0
DEP.12	0.04	0	0.2	0	0.06	0.09	0.05	0.11	0	0	0.23	0	0	0	0	0	0	0	0	0	0	0	0	0	0.03	0	0.05	0.05	0	0.07	0	0	0	0	0.06	0.06	0
DEP.13	0	0	0.14	0	0.07	0.05	0.07	0	0.18	0.23	0	0	0	0	0	0.09	0	0	0.06	0	0	0	0	0.05	0	0	0	0	0.04	0	0.03	0.05	0	0.03	0	0	0
PRO.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.12	-0.08	0	-0.17	0	0.2	0	0	0	0	0	0	0	0.12	-0.07	0	0.1	-0.12	0	0	0	0	0
HYP.1	0	0	0	0	0.14	0	0	0	0	0	0	0	0	0.05	0	0.09	-0.05	0.08	0	0	0.46	0	0	0	-0.04	0.11	0	-0.04	0	0	0.03	0.05	0	0.04	0	0	0
EMO.1	0	0.14	0	0	0.05	0	0	0	0	0	0	0	0.05	0	0.04	0.09	0	0	0.11	0	0	0	0	0.08	0	0	0.04	0	0	0	0	0	0	0	0.04	0	-0.04
PRO.2	-0.05	0	0	0	0	0	0	0	0	0	0	0.12	0	0.04	0	0	0	-0.1	0	0.11	0	0	-0.07	0	-0.09	0	0	0.14	-0.05	0	0.08	0	0	0	0	0	0
COND.1	0.08	0	0	0.05	0	0	0.03	-0.04	0.04	0	0.09	-0.08	0.09	0.09	0	0	0	0.17	0	0	0	-0.04	0.1	0.09	0	0	0	0	0.11	0	0	0.04	0	0	0	0	0
PEER.1	0	0.06	0	0	0	-0.06	0	0.08	0	0	0	0	-0.05	0	0	0	0	-0.07	0.04	0	0.04	0.09	0	0.07	0.13	0	0.1	0	0	0.04	-0.07	0	0	0.19	0	0	0.04
COND.2	0	0	0	0	0	0	0	0	0.04	0	0	-0.17	0.08	0	-0.1	0.17	-0.07	0	-0.03	-0.07	0	0.05	0	0	0.04	0	0	0	0.07	0	-0.07	0.08	0	0	0	0.08	0
EMO.2	0.05	0	0.07	0	0.03	0.04	0	0.06	-0.06	0	0.06	0	0	0.11	0	0	0.04	-0.03	0	0.06	0.04	0	0	0.2	0.04	0	0.1	0	0	0.06	0	0	-0.04	0	0.23	0	0.04
PRO.3	0	0	0	0	0	0	0	0	0	0	0	0.2	0	0	0.11	0	0	-0.07	0.06	0	0	-0.06	0	0	-0.04	0	0	0.15	0	0	0.18	0	0	0	0	0	0
HYP.2	0	0	0	0	0	0	0	0	0	0	0	0	0.46	0	0	0	0.04	0	0.04	0	0	0	0.07	0	0	0.14	0	0	0.05	0	0	0	0	0	0	0	0
PEER.2	0	0	0	0	0	0	0	0.05	0	0	0	0	0	0	0	-0.04	0.09	0.05	0	-0.06	0	0	0	0	0.26	0	0	0	0	0.05	0	0.05	0	0.09	0	0	0

COND.3	0	0	0	0	0	0	0	0	0.07	0	0	0	0	0	-0.07	0.1	0	0	0	0	0.07	0	0	0.04	0.04	0	0	-0.06	0.1	0.07	0	0	0.11	0	0	0	0
EMO.3	0.07	0	0	0.22	0	0.04	0	0.09	0.04	0	0.05	0	0	0.08	0	0.09	0.07	0	0.2	0	0	0	0.04	0	0	0	0	0	0	0.11	0	0	0	0	0.04	0	0
PEER.3	0	0	0	-0.05	0	0	0	0.08	0	0.03	0	0	-0.04	0	-0.09	0	0.13	0.04	0.04	-0.04	0	0.26	0.04	0	0	0	0	-0.08	0	0.2	-0.04	0.06	0	0.12	0	0.05	0.04
HYP.3	0	0	0	0	0.19	0	0	-0.05	0	0	0	0	0.11	0	0	0	0	0	0	0	0.14	0	0	0	0	0	0.08	0.07	0	0.05	0	0.1	0.04	0.04	0	0.41	-0.06
EMO.4	0	0	0	0	0	0	0	0	0	0.05	0	0	0	0.04	0	0	0.1	0	0.1	0	0	0	0	0	0	0.08	0	0	0	0	-0.07	0	0	0	0.28	0	0
PRO.4	-0.05	0	0	0	0	0	0	0	0	0.05	0	0.12	-0.04	0	0.14	0	0	0	0	0.15	0	0	-0.06	0	-0.08	0.07	0	0	0	0	0.12	0	0	0	0	-0.05	0
COND.4	0	0	0	0	0	0	0	0	0.04	0	0.04	-0.07	0	0	-0.05	0.11	0	0.07	0	0	0.05	0	0.1	0	0	0	0	0	0	0	0.05	0	0.07	0.27	0	0	0.05	-0.05
PEER.4	0	0	0	0	0	0	0	0.11	0	0.07	0	0	0	0	0	0	0.04	0	0.06	0	0	0.05	0.07	0.11	0.2	0.05	0	0	0.05	0	0.11	0	0	0.1	0.04	0	0
PRO.5	0	0	0	0	0	0	0	0	0	0	0.03	0.1	0.03	0	0.08	0	-0.07	-0.07	0	0.18	0	0	0	0	-0.04	0	-0.07	0.12	0	0.11	0	-0.1	0	0.1	0	-0.08	-0.08
HYP.4	0	0	0	0	0	0	0	0	0	0	0.05	-0.12	0.05	0	0	0.04	0	0.08	0	0	0	0.05	0	0	0.06	0.1	0	0	0.07	0	-0.1	0	0	-0.04	0	0.23	-0.05
COND.5	0	0	0	0	0	0	0.09	0	0	0	0	0	0	0	0	0	0	0	-0.04	0	0	0	0.11	0	0	0.04	0	0	0.27	0	0	0	0	0	0	0	0
PEER.5	0	0	0	0	0	0	0	0.04	0	0	0.03	0	0.04	0	0	0	0.19	0	0	0	0	0.09	0	0	0.12	0.04	0	0	0	0.1	0.1	-0.04	0	0	0.05	0	0
EMO.5	0	0	0	0	0	0	0.05	0	0	0.06	0	0	0	0.04	0	0	0	0	0.23	0	0	0	0	0.04	0	0	0.28	0	0	0.04	0	0	0	0.05	0	0	0
HYP.5	0	0	0	-0.05	0.08	-0.03	0	0	0	0.06	0	0	0	0	0	0	0	0.08	0	0	0	0	0	0	0.05	0.41	0	-0.05	0.05	0	-0.08	0.23	0	0	0	0	-0.05
EA	0	0	0	0	0	0	0	0	0	0	0	0	0	-0.04	0	0	0.04	0	0.04	0	0	0	0	0	0.04	-0.06	0	0	-0.05	0	-0.08	-0.05	0	0	0	-0.05	0

Supplementary Table 10: Anxiety PGS network matrix.

Node	DEP.2	DEP.3	DEP.5	DEP.6	DEP.7	DEP.8	DEP.9	DEP.10	DEP.11	DEP.12	DEP.13	PRO.1	HYP.1	EMO.1	PRO.2	COND.1	PEER.1	COND.2	EMO.2	PRO.3	HYP.2	PEER.2	COND.3	EMO.3	PEER.3	HYP.3	EMO.4	PRO.4	COND.4	PEER.4	PRO.5	HYP.4	COND.5	PEER.5	EMO.5	HYP.5	ANX
DEP.2	0	0.15	0.08	0.1	0.06	0.06	0	0	0.1	0	0.04	0	0	0	-0.05	0.08	0	0	0.05	0	0	0	0	0.07	0	0	0	-0.05	0	0	0	0	0	0	0	0	0
DEP.3	0.15	0	0	0.04	0.1	0	0	0.04	0	0	0	0	0	0.14	0	0	0.06	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
DEP.5	0.08	0	0	0.11	0.06	0.2	0.06	0.06	0.14	0.21	0.14	0	0	0	0	0	0	0	0.07	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
DEP.6	0.1	0.04	0.11	0	0.12	0.06	0	0.05	0	0	0	0	0	0	0	0.06	0	0	0	0	-0.04	0	0	0.22	-0.05	0	0	0	0	0	0	0	0	0.04	-0.05	0
DEP.7	0.06	0.1	0.06	0.12	0	0	0.05	0.06	0	0.06	0.05	0	0.14	0.05	0	0	0	0	0	0	0	0	0	0	0	0.2	0	0	0.04	0	0	0	0	0	0	0.07	0
DEP.8	0.06	0	0.2	0.06	0	0	0.35	0.08	0.15	0.1	0.04	0	0	0	0	0	-0.06	0	0.05	0	0	0	0	0.04	0	0	0	0	0	0	0	0	0	0	-0.04	0	0
DEP.9	0	0	0.06	0	0.05	0.35	0	0	0.13	0.06	0.08	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.09	0	0.07	0	0
DEP.10	0	0.04	0.06	0.05	0.06	0.08	0	0	0.17	0.12	0	0	0	0	0	-0.04	0.08	0	0.07	0	0	0.05	0	0.09	0.08	-0.04	0	0	0	0.11	0	0	0	0.04	0	0	0.04
DEP.11	0.1	0	0.14	0	0	0.15	0.13	0.17	0	0	0.18	0	0	0	0	0.05	0	0.04	-0.06	0	0	0	0.07	0.05	0	-0.03	0	0	0.05	0	0.03	0	0	0	0	0	0
DEP.12	0	0	0.21	0	0.06	0.1	0.06	0.12	0	0	0.23	0	0	0	0	0	0	0	0	0	0	0	0	0	0.03	0	0.05	0.05	0	0.07	0	0	0	0	0.07	0.05	0
DEP.13	0.04	0	0.14	0	0.05	0.04	0.08	0	0.18	0.23	0	0	0	0	0	0.1	0	0	0.06	0	0.03	0	0	0.05	0	0	0	0	0	0	0	0.04	0	0.03	0	0	0
PRO.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.12	-0.08	0	-0.17	0	0.2	0	0	0	0	0	0	0	0.12	-0.07	0	0.1	-0.12	0	0	0	0	0
HYP.1	0	0	0	0	0.14	0	0	0	0	0	0	0	0	0.05	0	0.09	-0.05	0.08	0	0	0.46	0	0	0	-0.04	0.11	0	-0.04	0	0	0.04	0.05	0	0.04	0	0	0
EMO.1	0	0.14	0	0	0.05	0	0	0	0	0	0	0	0.05	0	0.04	0.09	0	0	0.11	0	0	0	0	0.08	0	0	0.04	0	0	0	0	0	0	0	0.04	0	0
PRO.2	-0.05	0	0	0	0	0	0	0	0	0	0	0.12	0	0.04	0	0	0	-0.1	0	0.11	0	0	-0.07	0	-0.09	0	0	0.14	-0.05	0	0.08	0	0	0	0	0	0
COND.1	0.08	0	0	0.06	0	0	0	-0.04	0.05	0	0.1	-0.08	0.09	0.09	0	0	0	0.17	0	0	0	-0.04	0.1	0.09	0	0	0	0	0.11	0	0	0.04	0	0	0	0	0
PEER.1	0	0.06	0	0	0	-0.06	0	0.08	0	0	0	0	-0.05	0	0	0	0	-0.07	0.04	0	0.04	0.09	0	0.07	0.13	0	0.1	0	0	0.04	-0.08	0	0	0.19	0	0	0
COND.2	0	0	0	0	0	0	0	0	0.04	0	0	-0.17	0.08	0	-0.1	0.17	-0.07	0	-0.03	-0.07	0	0.05	0	0	0.04	0	0	0	0.07	0	-0.07	0.08	0	0	0	0.08	0
EMO.2	0.05	0	0.07	0	0	0.05	0	0.07	-0.06	0	0.06	0	0	0.11	0	0	0.04	-0.03	0	0.06	0.05	0	0	0.21	0.04	0	0.1	0	0	0.06	0	0	-0.04	0	0.24	0	0
PRO.3	0	0	0	0	0	0	0	0	0	0	0	0.2	0	0	0.11	0	0	-0.07	0.06	0	0	-0.06	0	0	-0.04	0	0	0.15	0	0	0.19	0	0	0	0	0	0
HYP.2	0	0	0	-0.04	0	0	0	0	0	0	0.03	0	0.46	0	0	0	0.04	0	0.05	0	0	0	0.07	0	0	0.14	0	0	0.05	0	0	0	0	0	0	0	0
PEER.2	0	0	0	0	0	0	0	0.05	0	0	0	0	0	0	0	-0.04	0.09	0.05	0	-0.06	0	0	0	0	0.26	0	0	0	0	0.05	0	0.05	0	0.09	0	0	0

COND.3	0	0	0	0	0	0	0	0	0.07	0	0	0	0	0	-0.07	0.1	0	0	0	0	0.07	0	0	0.04	0.04	0	0	-0.06	0.1	0.06	0	0	0.11	0.04	0	0	0
EMO.3	0.07	0	0	0.22	0	0.04	0	0.09	0.05	0	0.05	0	0	0.08	0	0.09	0.07	0	0.21	0	0	0	0.04	0	0	0	0	0	0	0.11	0	0	0	0	0	0	0
PEER.3	0	0	0	-0.05	0	0	0	0.08	0	0.03	0	0	-0.04	0	-0.09	0	0.13	0.04	0.04	-0.04	0	0.26	0.04	0	0	0	0	-0.08	0	0.2	-0.04	0.06	0	0.12	0	0.05	0
HYP.3	0	0	0	0	0.2	0	0	-0.04	-0.03	0	0	0	0.11	0	0	0	0	0	0	0	0.14	0	0	0	0	0	0.08	0.07	0	0.05	0	0.11	0.04	0.04	0	0.42	0
EMO.4	0	0	0	0	0	0	0	0	0	0.05	0	0	0	0.04	0	0	0.1	0	0.1	0	0	0	0	0	0	0.08	0	0	0	0	-0.07	0	0	0	0.28	0	0
PRO.4	-0.05	0	0	0	0	0	0	0	0	0.05	0	0.12	-0.04	0	0.14	0	0	0	0	0.15	0	0	-0.06	0	-0.08	0.07	0	0	0	0	0.12	0	0	0	0	-0.05	0
COND.4	0	0	0	0	0.04	0	0	0	0.05	0	0	-0.07	0	0	-0.05	0.11	0	0.07	0	0	0.05	0	0.1	0	0	0	0	0	0	0	0.05	0	0.08	0.27	0	0	0.05	0
PEER.4	0	0	0	0	0	0	0	0.11	0	0.07	0	0	0	0	0	0	0.04	0	0.06	0	0	0.05	0.06	0.11	0.2	0.05	0	0	0.05	0	0.11	0	0	0.09	0.05	0	0
PRO.5	0	0	0	0	0	0	0	0	0.03	0	0	0.1	0.04	0	0.08	0	-0.08	-0.07	0	0.19	0	0	0	0	-0.04	0	-0.07	0.12	0	0.11	0	-0.1	0	0.1	0	-0.07	0
HYP.4	0	0	0	0	0	0	0	0	0	0	0.04	-0.12	0.05	0	0	0.04	0	0.08	0	0	0	0.05	0	0	0.06	0.11	0	0	0.08	0	-0.1	0	0	-0.05	0	0.24	0
COND.5	0	0	0	0	0	0	0.09	0	0	0	0	0	0	0	0	0	0	0	-0.04	0	0	0	0.11	0	0	0.04	0	0	0.27	0	0	0	0	0	0	0	0	0
PEER.5	0	0	0	0	0	0	0	0.04	0	0	0.03	0	0.04	0	0	0	0.19	0	0	0	0	0.09	0.04	0	0.12	0.04	0	0	0	0.09	0.1	-0.05	0	0	0.06	0	0
EMO.5	0	0	0	0.04	0	-0.04	0.07	0	0	0.07	0	0	0	0.04	0	0	0	0	0.24	0	0	0	0	0	0	0	0.28	0	0	0.05	0	0	0	0.06	0	0	0
HYP.5	0	0	0	-0.05	0.07	0	0	0	0	0.05	0	0	0	0	0	0	0	0.08	0	0	0	0	0	0	0.05	0.42	0	-0.05	0.05	0	-0.07	0.24	0	0	0	0	0
ANX	0	0	0	0	0	0	0	0.04	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Supplementary Table 11: ADHD PGS network matrix.

Node	DEP .2	DEP .3	DEP .5	DEP .6	DEP .7	DEP .8	DEP .9	DEP. 10	DEP. 11	DEP. 12	DEP. 13	PRO .1	HYP .1	EMO .1	PRO .2	COND .1	PEER .1	COND .2	EMO .2	PRO .3	HYP .2	PEER .2	COND .3	EMO .3	PEER .3	HYP .3	EMO .4	PRO .4	COND .4	PEER .4	PRO .5	HYP .4	COND .5	PEER .5	EMO .5	HYP .5	ADHD
DEP.2	0	0.15	0.08	0.1	0.06	0.06	0	0	0.1	0	0.04	0	0	0	-0.05	0.08	0	0	0.05	0	0	0	0	0.07	0	0	0	-0.05	0	0	0	0	0	0	0	0	0
DEP.3	0.15	0	0	0.04	0.1	0	0	0.04	0	0	0	0	0	0.14	0	0	0.06	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
DEP.5	0.08	0	0	0.12	0.06	0.2	0.06	0.06	0.14	0.21	0.14	0	0	0	0	0	0	0	0.07	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
DEP.6	0.1	0.04	0.12	0	0.12	0.06	0	0.05	0	0	0	0	0	0	0	0.06	0	0	0	0	-0.03	0	0	0.22	-0.05	0	0	0	0	0	0	0	0	0.04	-0.05	0
DEP.7	0.06	0.1	0.06	0.12	0	0	0.05	0.06	0	0.07	0.05	0	0.13	0.05	0	0	0	0	0	0	0	0	0	0	0	0.2	0	0	0.04	0	0	0	0	0	0	0.07	0
DEP.8	0.06	0	0.2	0.06	0	0	0.35	0.07	0.15	0.1	0.04	0	0	0	0	0	-0.06	0	0.04	0	0	0	0	0.04	0	0	0	0	0	0	0	0	0	0	0	0	0
DEP.9	0	0	0.06	0	0.05	0.35	0	0.04	0.12	0.05	0.08	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.09	0	0.05	0	0
DEP.10	0	0.04	0.06	0.05	0.06	0.07	0.04	0	0.16	0.12	0	0	0	0	0	-0.04	0.08	0	0.07	0	0	0.05	0	0.09	0.08	-0.04	0	0	0	0.11	0	0	0	0.04	0	0	0
DEP.11	0.1	0	0.14	0	0	0.15	0.12	0.16	0	0	0.18	0	0	0	0	0.05	0	0.04	-0.06	0	0	0	0.07	0.05	0	-0.03	0	0	0.05	0	0.03	0	0	0	0	0	0
DEP.12	0	0	0.21	0	0.07	0.1	0.05	0.12	0	0	0.23	0	0	0	0	0	0	0	0	0	0	0	0	0	0.03	0	0.05	0.05	0	0.07	0	0	0	0	0.06	0.05	0
DEP.13	0.04	0	0.14	0	0.05	0.04	0.08	0	0.18	0.23	0	0	0.03	0	0	0.1	0	0	0.06	0	0	0	0	0.05	0	0	0	0	0	0	0	0.04	0	0.03	0	0	0
PRO.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.12	-0.08	0	-0.17	0	0.2	0	0	0	0	0	0	0	0.12	-0.07	0	0.1	-0.12	0	0	0	0	0
HYP.1	0	0	0	0	0.13	0	0	0	0	0	0.03	0	0	0.05	0	0.09	-0.05	0.08	0	0	0.46	0	0	0	-0.04	0.11	0	-0.04	0	0	0.04	0.05	0	0.04	0	0	0
EMO.1	0	0.14	0	0	0.05	0	0	0	0	0	0	0	0.05	0	0.04	0.09	0	0	0.11	0	0	0	0	0.08	0	0	0.04	0	0	0	0	0	0	0	0.04	0	0
PRO.2	-0.05	0	0	0	0	0	0	0	0	0	0	0.12	0	0.04	0	0	0	-0.1	0	0.11	0	0	-0.07	0	-0.09	0	0	0.14	-0.05	0	0.08	0	0	0	0	0	0
COND.1	0.08	0	0	0.06	0	0	0	-0.04	0.05	0	0.1	-0.08	0.09	0.09	0	0	0	0.17	0	0	0	-0.04	0.1	0.09	0	0	0	0	0.11	0	0	0.04	0	0	0	0	0
PEER.1	0	0.06	0	0	0	-0.06	0	0.08	0	0	0	0	-0.05	0	0	0	0	-0.07	0.04	0	0.04	0.09	0	0.07	0.13	0	0.1	0	0	0.04	-0.08	0	0	0.19	0	0	0
COND.2	0	0	0	0	0	0	0	0	0.04	0	0	-0.17	0.08	0	-0.1	0.17	-0.07	0	-0.03	-0.07	0	0.05	0	0	0.04	0	0	0	0.07	0	-0.07	0.08	0	0	0	0.08	0
EMO.2	0.05	0	0.07	0	0	0.04	0	0.07	-0.06	0	0.06	0	0	0.11	0	0	0.04	-0.03	0	0.06	0.05	0	0	0.21	0.04	0	0.1	0	0	0.06	0	0	-0.04	0	0.24	0	0
PRO.3	0	0	0	0	0	0	0	0	0	0	0	0.2	0	0	0.11	0	0	-0.07	0.06	0	0	-0.06	0	0	-0.04	0	0	0.15	0	0	0.19	0	0	0	0	0	0
HYP.2	0	0	0	-0.03	0	0	0	0	0	0	0	0	0.46	0	0	0	0.04	0	0.05	0	0	0	0.07	0	0	0.14	0	0	0.05	0	0	0	0	0	0	0	0
PEER.2	0	0	0	0	0	0	0	0.05	0	0	0	0	0	0	0	-0.04	0.09	0.05	0	-0.06	0	0	0	0	0.26	0	0	0	0	0.05	0	0.05	0	0.09	0	0	0

COND.3	0	0	0	0	0	0	0	0	0.07	0	0	0	0	0	-0.07	0.1	0	0	0	0	0.07	0	0	0.04	0.04	0	0	-0.06	0.09	0.06	0	0	0.11	0.04	0	0	0
EMO.3	0.07	0	0	0.22	0	0.04	0	0.09	0.05	0	0.05	0	0	0.08	0	0.09	0.07	0	0.21	0	0	0	0.04	0	0	0	0	0	0	0.11	0	0	0	0	0	0	0
PEER.3	0	0	0	-0.05	0	0	0	0.08	0	0.03	0	0	-0.04	0	-0.09	0	0.13	0.04	0.04	-0.04	0	0.26	0.04	0	0	0	0	-0.08	0	0.2	-0.04	0.06	0	0.12	0	0.05	0
HYP.3	0	0	0	0	0.2	0	0	-0.04	-0.03	0	0	0	0.11	0	0	0	0	0	0	0	0.14	0	0	0	0	0	0.08	0.07	0	0.05	0	0.11	0.03	0.04	0	0.41	0.07
EMO.4	0	0	0	0	0	0	0	0	0	0.05	0	0	0	0.04	0	0	0.1	0	0.1	0	0	0	0	0	0	0.08	0	0	0	0	-0.07	0	0	0	0.28	0	0
PRO.4	-0.05	0	0	0	0	0	0	0	0	0.05	0	0.12	-0.04	0	0.14	0	0	0	0	0.15	0	0	-0.06	0	-0.08	0.07	0	0	0	0	0.12	0	0	0	0	-0.05	0
COND.4	0	0	0	0	0.04	0	0	0	0.05	0	0	-0.07	0	0	-0.05	0.11	0	0.07	0	0	0.05	0	0.09	0	0	0	0	0	0	0.05	0	0.08	0.27	0	0	0.05	0.05
PEER.4	0	0	0	0	0	0	0	0.11	0	0.07	0	0	0	0	0	0	0.04	0	0.06	0	0	0.05	0.06	0.11	0.2	0.05	0	0	0.05	0	0.11	0	0	0.09	0.05	0	0
PRO.5	0	0	0	0	0	0	0	0	0.03	0	0	0.1	0.04	0	0.08	0	-0.08	-0.07	0	0.19	0	0	0	0	-0.04	0	-0.07	0.12	0	0.11	0	-0.1	0	0.1	0	-0.07	0
HYP.4	0	0	0	0	0	0	0	0	0	0	0.04	-0.12	0.05	0	0	0.04	0	0.08	0	0	0	0.05	0	0	0.06	0.11	0	0	0.08	0	-0.1	0	0	-0.05	0	0.24	0
COND.5	0	0	0	0	0	0	0.09	0	0	0	0	0	0	0	0	0	0	0	-0.04	0	0	0	0.11	0	0	0.03	0	0	0.27	0	0	0	0	0	0	0	0
PEER.5	0	0	0	0	0	0	0	0.04	0	0	0.03	0	0.04	0	0	0	0.19	0	0	0	0	0.09	0.04	0	0.12	0.04	0	0	0	0.09	0.1	-0.05	0	0	0.05	0	0
EMO.5	0	0	0	0.04	0	0	0.05	0	0	0.06	0	0	0	0.04	0	0	0	0	0.24	0	0	0	0	0	0	0	0.28	0	0	0.05	0	0	0	0.05	0	0	0
HYP.5	0	0	0	-0.05	0.07	0	0	0	0	0.05	0	0	0	0	0	0	0	0.08	0	0	0	0	0	0	0.05	0.41	0	-0.05	0.05	0	-0.07	0.24	0	0	0	0	0
ADHD	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.07	0	0	0.05	0	0	0	0	0	0	0	0

Supplementary Table 12: All PGSs network matrix.

Node	DEP.2	DEP.3	DEP.5	DEP.6	DEP.7	DEP.8	DEP.9	DEP.10	DEP.11	DEP.12	DEP.13	PRO.1	HYP.1	EMO.1	PRO.2	COND.1	PEER.1	COND.2	EMO.2	PRO.3	HYP.2	PEER.2	COND.3	EMO.3	PEER.3	HYP.3	EMO.4	PRO.4	COND.4	PEER.4	PRO.5	HYP.4	COND.5	PEER.5	EMO.5	HYP.5	BMI	EA	DEP	ANX	ADHD
DEP.2	0	0.15	0.08	0.09	0.07	0.06	0	0	0.1	0	0.04	0	0	0	-0.05	0.08	0	0	0.05	0	0	0	0	0.07	0	0	0	-0.04	0	0	0	0	0	0	0	0	0	0	0	0	0
DEP.3	0.15	0	0	0.04	0.1	0	0	0.04	0	0	0	0	0	0.14	0	0	0.06	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
DEP.5	0.08	0	0	0.11	0.06	0.2	0.06	0.06	0.14	0.21	0.14	0	0	0	0	0	0	0	0.07	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
DEP.6	0.09	0.04	0.11	0	0.11	0.06	0	0.05	0	0	0	0	0	0	0	0.06	0	0	0	0	0	0	0	0.22	-0.05	0	0	0	0	0	0	0	0	0	0.04	-0.06	0	0	0	0	0
DEP.7	0.07	0.1	0.06	0.11	0	0	0.05	0.06	0	0.07	0.06	0	0.14	0.05	0	0	0	0	0	0	0	0	0	0	0	0.2	0	0	0	0	0	0	0	0	0	0.07	0	0	0	0	0
DEP.8	0.06	0	0.2	0.06	0	0	0.35	0.07	0.15	0.09	0.04	0	0	0	0	0	-0.05	0	0.04	0	0	0	0	0.04	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
DEP.9	0	0	0.06	0	0.05	0.35	0	0.04	0.12	0.05	0.07	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.09	0	0.05	0	0	0	0	0	0
DEP.10	0	0.04	0.06	0.05	0.06	0.07	0.04	0	0.16	0.12	0	0	0	0	0	-0.04	0.08	0	0.07	0	0	0.05	0	0.09	0.07	-0.04	0	0	0	0.11	0	0	0	0.05	0	0	0	0	0	0	0	0
DEP.11	0.1	0	0.14	0	0	0.15	0.12	0.16	0	0	0.18	0	0	0	0	0.05	0	0.03	-0.07	0	0	0	0.08	0.05	0	-0.03	0	0	0	0.04	0	0	0	0	0	0	0	0	0	0	0
DEP.12	0	0	0.21	0	0.07	0.09	0.05	0.12	0	0	0.23	0	0	0	0	0	0	0	0	0	0	0	0	0	0.04	0	0.05	0.05	0	0.07	0	0	0	0	0.06	0.05	0	0	0	0	0
DEP.13	0.04	0	0.14	0	0.06	0.04	0.07	0	0.18	0.23	0	0	0	0	0	0.1	0	0	0.07	0	0	0	0	0.05	0	0	0	0	0.04	0	0.04	0.05	0	0	0	0	0	0	0	0	0
PRO.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.12	-0.08	0	-0.17	0	0.2	0	0	0	0	0	0	0	0.12	-0.07	0	0.1	-0.12	0	0	0	0	0	0	0	0	0
HYP.1	0	0	0	0	0.14	0	0	0	0	0	0	0	0	0.05	0	0.1	-0.05	0.08	0	0	0.46	0	0	0	-0.03	0.11	0	-0.04	0	0	0.03	0.05	0	0.04	0	0	0	0	0	0	0
EMO.1	0	0.14	0	0	0.05	0	0	0	0	0	0	0	0.05	0	0.04	0.09	0	0	0.11	0	0	0	0	0.08	0	0	0.04	0	0	0	0	0	0	0	0.04	0	0	-0.04	0	0	0
PRO.2	-0.05	0	0	0	0	0	0	0	0	0	0	0.12	0	0.04	0	0	0	-0.1	0	0.11	0	0	-0.07	0	-0.09	0	0	0.14	-0.05	0	0.08	0	0	0	0	0	0	0	0	0	0
CONDD.1	0.08	0	0	0.06	0	0	0	-0.04	0.05	0	0.1	-0.08	0.1	0.09	0	0	0	0.17	0	0	0	-0.04	0.11	0.09	0	0	0	0	0.11	0	0	0.04	0	0	0	0	0	0	0	0	0
PEER.1	0	0.06	0	0	0	-0.05	0	0.08	0	0	0	0	-0.05	0	0	0	0	-0.07	0.05	0	0.04	0.09	0	0.06	0.13	0	0.1	0	0	0.04	-0.07	0	0	0.19	0	0	0	0.04	0	0	0
CONDD.2	0	0	0	0	0	0	0	0	0.03	0	0	-0.17	0.08	0	-0.1	0.17	-0.07	0	0	-0.07	0	0.05	0	0	0.04	0	0	0	0.07	0	-0.07	0.08	0	0	0	0.08	0	0	0	0	0
EMO.2	0.05	0	0.07	0	0	0.04	0	0.07	-0.07	0	0.07	0	0	0.11	0	0	0.05	0	0	0.06	0.05	0	0	0.21	0	0	0.1	0	0	0.06	0	0	-0.04	0	0.23	0	0	0.04	0.03	0	0
PRO.3	0	0	0	0	0	0	0	0	0	0	0	0.2	0	0	0.11	0	0	-0.07	0.06	0	0	-0.06	0	0	-0.04	0	0	0.15	0	0	0.18	0	0	0	0	0	0	0	0	0	0
HYP.2	0	0	0	0	0	0	0	0	0	0	0	0	0.46	0	0	0	0.04	0	0.05	0	0	0	0.07	0	0	0.14	0	0	0.05	0	0	0	0	0	0	0	0	0	0	0	0
PEER.2	0	0	0	0	0	0	0	0.05	0	0	0	0	0	0	0	-0.04	0.09	0.05	0	-0.06	0	0	0	0	0.26	0	0	0	0	0.05	0	0.05	0	0.09	0	0	0	0	0	0	0

COND.3	0	0	0	0	0	0	0	0	0.08	0	0	0	0	0	-0.07	0.11	0	0	0	0	0.07	0	0	0.04	0	0	0	-0.07	0.1	0.07	0	0	0.11	0.05	0	0	0	0	0	0	0
EMO.3	0.07	0	0	0.22	0	0.04	0	0.09	0.05	0	0.05	0	0	0.08	0	0.09	0.06	0	0.21	0	0	0	0.04	0	0.04	0	0	0	0	0.1	0	0	0	0	0	0	0	0	0	0	0
PEER.3	0	0	0	-0.05	0	0	0	0.07	0	0.04	0	0	-0.03	0	-0.09	0	0.13	0.04	0	-0.04	0	0.26	0	0.04	0	0	0	-0.08	0	0.2	-0.04	0.06	0	0.12	0	0.05	0	0.04	0	0	0
HYP.3	0	0	0	0	0.2	0	0	-0.04	-0.03	0	0	0	0.11	0	0	0	0	0	0	0	0.14	0	0	0	0	0	0.08	0.07	0	0.05	0	0.1	0.04	0.04	0	0.41	0	-0.05	0	0	0.05
EMO.4	0	0	0	0	0	0	0	0	0	0.05	0	0	0	0.04	0	0	0.1	0	0.1	0	0	0	0	0	0	0.08	0	0	0	0	-0.07	0	0	0	0.28	0	0	0	0	0	0
PRO.4	-0.04	0	0	0	0	0	0	0	0	0.05	0	0.12	-0.04	0	0.14	0	0	0	0	0.15	0	0	-0.07	0	-0.08	0.07	0	0	0	0	0.12	0	0	0	0	-0.05	0	0	0	0	0
COND.4	0	0	0	0	0	0	0	0	0.04	0	0.04	-0.07	0	0	-0.05	0.11	0	0.07	0	0	0.05	0	0.1	0	0	0	0	0	0	0.05	0	0.07	0.27	0	0	0.05	0	-0.04	0	0	0.04
PEER.4	0	0	0	0	0	0	0	0.11	0	0.07	0	0	0	0	0	0	0.04	0	0.06	0	0	0.05	0.07	0.1	0.2	0.05	0	0	0.05	0	0.1	0	0	0.09	0.05	0	0.05	0	0.04	0	0
PRO.5	0	0	0	0	0	0	0	0	0	0	0.04	0.1	0.03	0	0.08	0	-0.07	-0.07	0	0.18	0	0	0	0	-0.04	0	-0.07	0.12	0	0.1	0	-0.1	0	0.1	0	-0.08	0.05	-0.06	0	0	0
HYP.4	0	0	0	0	0	0	0	0	0	0	0.05	-0.12	0.05	0	0	0.04	0	0.08	0	0	0	0.05	0	0	0.06	0.1	0	0	0.07	0	-0.1	0	0	-0.04	0	0.23	0	-0.05	0	0	0
COND.5	0	0	0	0	0	0	0.09	0	0	0	0	0	0	0	0	0	0	0	-0.04	0	0	0	0.11	0	0	0.04	0	0	0.27	0	0	0	0	0	0	0	0.04	0	0	0	0
PEER.5	0	0	0	0	0	0	0	0.05	0	0	0	0	0.04	0	0	0	0.19	0	0	0	0	0.09	0.05	0	0.12	0.04	0	0	0	0.09	0.1	-0.04	0	0	0.06	0	0	0	0	0	0
EMO.5	0	0	0	0.04	0	0	0.05	0	0	0.06	0	0	0	0.04	0	0	0	0	0.23	0	0	0	0	0	0	0	0.28	0	0	0.05	0	0	0	0.06	0	0	-0.04	0	0	0	0
HYP.5	0	0	0	-0.06	0.07	0	0	0	0	0.05	0	0	0	0	0	0	0	0.08	0	0	0	0	0	0	0.05	0.41	0	-0.05	0.05	0	-0.08	0.23	0	0	0	0	0	-0.05	0	0	0
BMI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.05	0.05	0	0.04	0	-0.04	0	0	-0.17	0	0	0.08
EA	0	0	0	0	0	0	0	0	0	0	0	0	0	-0.04	0	0	0.04	0	0.04	0	0	0	0	0	0.04	-0.05	0	0	-0.04	0	-0.06	-0.05	0	0	0	-0.05	-0.17	0	-0.06	0	-0.17
GDEP	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.03	0	0	0	0	0	0	0	0	0	0	0.04	0	0	0	0	0	0	0	-0.06	0	0.38	0.15
ANX	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.38	0	0
ADHD	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.05	0	0	0.04	0	0	0	0	0	0	0	0.08	-0.17	0.15	0	0

Supplementary Table 13: Phenotypic network matrix.

Node	DEP.2	DEP.3	DEP.5	DEP.6	DEP.7	DEP.8	DEP.9	DEP.10	DEP.11	DEP.12	DEP.13	PRO.1	HYP.1	EMO.1	PRO.2	COND.1	PEER.1	COND.2	EMO.2	PRO.3	HYP.2	PEER.2	COND.3	EMO.3	PEER.3	HYP.3	EMO.4	PRO.4	COND.4	PEER.4	PRO.5	HYP.4	COND.5	PEER.5	EMO.5	HYP.5
DEP.2	0	0.15	0.08	0.1	0.06	0.06	0	0	0.1	0	0.04	0	0	0	-0.05	0.07	0	0	0.05	0	0	0	0	0.07	0	0	0	-0.04	0	0	0	0	0	0	0	0
DEP.3	0.15	0	0	0.04	0.1	0	0	0.04	0	0	0	0	0	0.14	0	0	0.06	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
DEP.5	0.08	0	0	0.12	0.06	0.2	0.06	0.06	0.14	0.21	0.14	0	0	0	0	0	0	0	0.07	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
DEP.6	0.1	0.04	0.12	0	0.12	0.06	0	0.05	0	0	0	0	0	0	0	0.06	0	0	0	0	-0.04	0	0	0.22	-0.05	0	0	0	0	0	0	0	0	0	0.04	-0.05
DEP.7	0.06	0.1	0.06	0.12	0	0	0.05	0.06	0	0.07	0.05	0	0.14	0.05	0	0	0	0	0	0	0	0	0	0	0	0.2	0	0	0.04	0	0	0	0	0	0	0.07
DEP.8	0.06	0	0.2	0.06	0	0	0.35	0.07	0.15	0.1	0.04	0	0	0	0	0	-0.06	0	0.04	0	0	0	0	0.04	0	0	0	0	0	0	0	0	0	0	0	0
DEP.9	0	0	0.06	0	0.05	0.35	0	0.04	0.12	0.05	0.07	0	0	0	0	0.03	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.09	0	0.05	0
DEP.10	0	0.04	0.06	0.05	0.06	0.07	0.04	0	0.16	0.12	0	0	0	0	0	-0.04	0.08	0	0.07	0	0	0.05	0	0.09	0.08	-0.04	0	0	0	0.11	0	0	0	0.04	0	0
DEP.11	0.1	0	0.14	0	0	0.15	0.12	0.16	0	0	0.18	0	0	0	0	0.04	0	0.05	-0.07	0	0	0	0.07	0.05	0	-0.03	0	0	0.05	0	0.03	0	0	0	0	0
DEP.12	0	0	0.21	0	0.07	0.1	0.05	0.12	0	0	0.23	0	0	0	0	0	0	-0.03	0	0	0	0	0	0	0.04	0	0.05	0.05	0	0.07	0	0	0	0	0.06	0.06
DEP.13	0.04	0	0.14	0	0.05	0.04	0.07	0	0.18	0.23	0	0	0	0	0	0.09	0	0	0.06	0	0.03	0	0	0.05	0	0	0	0	0	0	0	0.04	0	0.03	0	0
PRO.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.12	-0.08	0	-0.17	0	0.2	0	0	0	0	0	0	0	0	0.12	-0.07	0	0.1	-0.12	0	0	0
HYP.1	0	0	0	0	0.14	0	0	0	0	0	0	0	0	0.05	0	0.09	-0.05	0.08	0	0	0.46	0	0	0	-0.04	0.11	0	-0.04	0	0	0.04	0.05	0	0.04	0	0
EMO.1	0	0.14	0	0	0.05	0	0	0	0	0	0	0	0.05	0	0.04	0.09	0	0	0.11	0	0	0	0	0.08	0	0	0.04	0	0	0	0	0	0	0	0.04	0
PRO.2	-0.05	0	0	0	0	0	0	0	0	0	0	0.12	0	0.04	0	0	0	-0.1	0	0.11	0	0	-0.07	0	-0.09	0	0	0.14	-0.05	0	0.08	0	0	0	0	0
COND.1	0.07	0	0	0.06	0	0	0.03	-0.04	0.04	0	0.09	-0.08	0.09	0.09	0	0	0	0.17	0	0	0	-0.04	0.1	0.09	0	0	0	0	0.11	0	0	0.04	0	0	0	0
PEER.1	0	0.06	0	0	0	-0.06	0	0.08	0	0	0	0	-0.05	0	0	0	0	-0.07	0.05	0	0.04	0.09	0	0.07	0.13	0	0.1	0	0	0.04	-0.08	0	0	0.19	0	0
COND.2	0	0	0	0	0	0	0	0	0.05	-0.03	0	-0.17	0.08	0	-0.1	0.17	-0.07	0	0	-0.07	0	0.05	0	0	0.04	0	0	0	0.07	0	-0.07	0.09	0	0	0	0.08
EMO.2	0.05	0	0.07	0	0	0.04	0	0.07	-0.07	0	0.06	0	0	0.11	0	0	0.05	0	0	0.07	0.04	0	0	0.21	0.03	0	0.1	0	0	0.06	0	0	-0.04	0	0.24	0
PRO.3	0	0	0	0	0	0	0	0	0	0	0	0.2	0	0	0.11	0	0	-0.07	0.07	0	0	-0.06	0	0	-0.04	0	0	0.15	0	0	0.19	0	0	0	0	0
HYP.2	0	0	0	-0.04	0	0	0	0	0	0	0.03	0	0.46	0	0	0	0.04	0	0.04	0	0	0	0.07	0	0	0.14	0	0	0.05	0	0	0	0	0	0	0
PEER.2	0	0	0	0	0	0	0	0.05	0	0	0	0	0	0	0	-0.04	0.09	0.05	0	-0.06	0	0	0	0	0.26	0	0	0	0	0.05	0	0.05	0	0.09	0	0

COND.3	0	0	0	0	0	0	0	0	0.07	0	0	0	0	0	-0.07	0.1	0	0	0	0	0.07	0	0	0.04	0.04	0	0	-0.06	0.1	0.06	0	0	0.11	0.04	0	0
EMO.3	0.07	0	0	0.22	0	0.04	0	0.09	0.05	0	0.05	0	0	0.08	0	0.09	0.07	0	0.21	0	0	0	0.04	0	0	0	0	0	0	0.11	0	0	0	0	0	0
PEER.3	0	0	0	-0.05	0	0	0	0.08	0	0.04	0	0	-0.04	0	-0.09	0	0.13	0.04	0.03	-0.04	0	0.26	0.04	0	0	0	0	-0.08	0	0.2	-0.04	0.06	0	0.12	0	0.05
HYP.3	0	0	0	0	0.2	0	0	-0.04	-0.03	0	0	0	0.11	0	0	0	0	0	0	0	0.14	0	0	0	0	0	0.08	0.07	0	0.05	0	0.11	0.04	0.04	0	0.42
EMO.4	0	0	0	0	0	0	0	0	0	0.05	0	0	0	0.04	0	0	0.1	0	0.1	0	0	0	0	0	0	0.08	0	0	0	0	-0.07	0	0	0	0.28	0
PRO.4	-0.04	0	0	0	0	0	0	0	0	0.05	0	0.12	-0.04	0	0.14	0	0	0	0	0.15	0	0	-0.06	0	-0.08	0.07	0	0	0	0	0.12	0	0	0	0	-0.05
COND.4	0	0	0	0	0.04	0	0	0	0.05	0	0	-0.07	0	0	-0.05	0.11	0	0.07	0	0	0.05	0	0.1	0	0	0	0	0	0	0	0.05	0	0.08	0.27	0	0	0.05
PEER.4	0	0	0	0	0	0	0	0.11	0	0.07	0	0	0	0	0	0	0.04	0	0.06	0	0	0.05	0.06	0.11	0.2	0.05	0	0	0.05	0	0.11	0	0	0.09	0.05	0
PRO.5	0	0	0	0	0	0	0	0	0.03	0	0	0.1	0.04	0	0.08	0	-0.08	-0.07	0	0.19	0	0	0	0	-0.04	0	-0.07	0.12	0	0.11	0	-0.1	0	0.1	0	-0.07
HYP.4	0	0	0	0	0	0	0	0	0	0	0.04	-0.12	0.05	0	0	0.04	0	0.09	0	0	0	0	0.05	0	0	0.06	0.11	0	0	0.08	0	-0.1	0	0	-0.05	0	0.23
COND.5	0	0	0	0	0	0	0.09	0	0	0	0	0	0	0	0	0	0	0	-0.04	0	0	0	0.11	0	0	0.04	0	0	0.27	0	0	0	0	0	0	0	0
PEER.5	0	0	0	0	0	0	0	0.04	0	0	0.03	0	0.04	0	0	0	0.19	0	0	0	0	0.09	0.04	0	0.12	0.04	0	0	0	0.09	0.1	-0.05	0	0	0.06	0
EMO.5	0	0	0	0.04	0	0	0.05	0	0	0.06	0	0	0	0.04	0	0	0	0	0.24	0	0	0	0	0	0	0	0.28	0	0	0.05	0	0	0	0.06	0	0
HYP.5	0	0	0	-0.05	0.07	0	0	0	0	0.06	0	0	0	0	0	0	0	0.08	0	0	0	0	0	0	0	0.05	0.42	0	-0.05	0.05	0	-0.07	0.23	0	0	0	0

Supplementary Table 14: Covariate-adjusted correlations between polygenic scores and scale items

Polygenic score	Item	Correlation estimate	P-value	FDR corrected p-value (38 tests)
BMI	DEP.1	0.007	0.595	0.628
BMI	DEP.2	0.035	0.008	0.020
BMI	DEP.3	0.030	0.025	0.049
BMI	DEP.4	0.024	0.079	0.121
BMI	DEP.5	0.018	0.191	0.259
BMI	DEP.6	0.025	0.064	0.101
BMI	DEP.7	0.048	0.000	0.002
BMI	DEP.8	0.029	0.033	0.063
BMI	DEP.9	0.039	0.004	0.011
BMI	DEP.10	0.026	0.053	0.088
BMI	DEP.11	0.048	0.000	0.002
BMI	DEP.12	0.033	0.015	0.034
BMI	DEP.13	0.017	0.218	0.276
BMI	PRO.1	-0.021	0.114	0.160
BMI	HYP.1	0.009	0.481	0.546
BMI	EMO.1	0.039	0.003	0.010
BMI	PRO.2	-0.009	0.488	0.546
BMI	COND.1	0.046	0.001	0.004
BMI	PEER.1	0.016	0.236	0.289
BMI	COND.2	0.023	0.087	0.127
BMI	EMO.2	-0.017	0.206	0.270
BMI	PRO.3	0.010	0.462	0.546
BMI	HYP.2	0.008	0.562	0.611
BMI	PEER.2	0.028	0.041	0.071
BMI	COND.3	0.036	0.007	0.017
BMI	EMO.3	0.041	0.002	0.008
BMI	PEER.3	0.031	0.022	0.047
BMI	HYP.3	0.042	0.002	0.007
BMI	EMO.4	-0.005	0.688	0.688
BMI	PRO.4	-0.007	0.614	0.630
BMI	COND.4	0.053	0.000	0.001
BMI	PEER.4	0.066	0.000	0.000
BMI	PRO.5	0.072	0.000	0.000
BMI	HYP.4	0.041	0.002	0.008
BMI	COND.5	0.057	0.000	0.000
BMI	PEER.5	0.042	0.002	0.007
BMI	EMO.5	-0.027	0.041	0.071
BMI	HYP.5	0.044	0.001	0.006
ANX	DEP.1	0.027	0.045	0.146

ANX	DEP.2	0.012	0.380	0.601
ANX	DEP.3	0.018	0.175	0.349
ANX	DEP.4	0.019	0.154	0.342
ANX	DEP.5	0.012	0.375	0.601
ANX	DEP.6	0.021	0.124	0.315
ANX	DEP.7	0.033	0.013	0.072
ANX	DEP.8	0.031	0.023	0.107
ANX	DEP.9	0.035	0.008	0.053
ANX	DEP.10	0.050	0.000	0.004
ANX	DEP.11	0.020	0.137	0.326
ANX	DEP.12	0.044	0.001	0.012
ANX	DEP.13	0.005	0.737	0.800
ANX	PRO.1	0.006	0.656	0.746
ANX	HYP.1	-0.002	0.869	0.917
ANX	EMO.1	0.027	0.046	0.146
ANX	PRO.2	-0.006	0.667	0.746
ANX	COND.1	0.008	0.551	0.697
ANX	PEER.1	0.016	0.237	0.449
ANX	COND.2	0.009	0.515	0.675
ANX	EMO.2	0.042	0.002	0.019
ANX	PRO.3	0.011	0.422	0.612
ANX	HYP.2	0.008	0.568	0.697
ANX	PEER.2	0.014	0.302	0.540
ANX	COND.3	0.001	0.958	0.958
ANX	EMO.3	0.014	0.312	0.540
ANX	PEER.3	0.011	0.435	0.612
ANX	HYP.3	0.011	0.412	0.612
ANX	EMO.4	0.022	0.108	0.293
ANX	PRO.4	0.023	0.085	0.249
ANX	COND.4	0.040	0.003	0.024
ANX	PEER.4	0.051	0.000	0.004
ANX	PRO.5	0.030	0.025	0.107
ANX	HYP.4	0.010	0.452	0.614
ANX	COND.5	0.001	0.921	0.946
ANX	PEER.5	0.027	0.042	0.146
ANX	EMO.5	0.019	0.162	0.342
ANX	HYP.5	0.006	0.640	0.746
ADHD	DEP.1	0.046	0.001	0.002
ADHD	DEP.2	0.012	0.366	0.480
ADHD	DEP.3	0.010	0.462	0.548
ADHD	DEP.4	0.059	0.000	0.000
ADHD	DEP.5	0.020	0.131	0.199

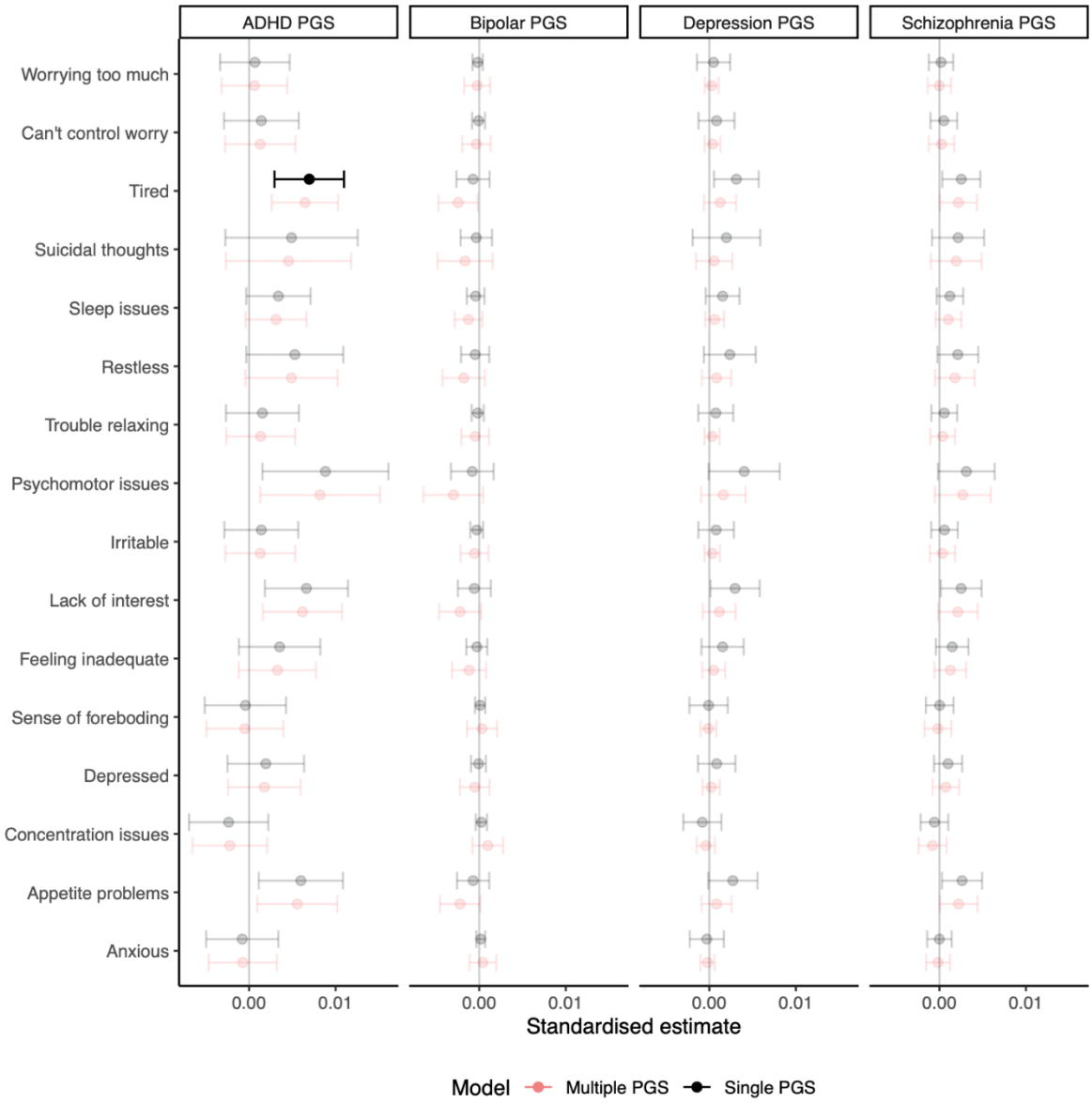
ADHD	DEP.6	0.017	0.218	0.296
ADHD	DEP.7	0.055	0.000	0.000
ADHD	DEP.8	0.001	0.915	0.921
ADHD	DEP.9	0.017	0.213	0.296
ADHD	DEP.10	0.040	0.003	0.007
ADHD	DEP.11	0.021	0.120	0.190
ADHD	DEP.12	0.042	0.002	0.004
ADHD	DEP.13	0.025	0.067	0.115
ADHD	PRO.1	-0.061	0.000	0.000
ADHD	HYP.1	0.073	0.000	0.000
ADHD	EMO.1	0.036	0.008	0.016
ADHD	PRO.2	-0.027	0.047	0.086
ADHD	COND.1	0.071	0.000	0.000
ADHD	PEER.1	0.001	0.921	0.921
ADHD	COND.2	0.072	0.000	0.000
ADHD	EMO.2	0.002	0.863	0.911
ADHD	PRO.3	0.003	0.825	0.895
ADHD	HYP.2	0.058	0.000	0.000
ADHD	PEER.2	0.010	0.443	0.543
ADHD	COND.3	0.060	0.000	0.000
ADHD	EMO.3	0.018	0.189	0.276
ADHD	PEER.3	0.055	0.000	0.000
ADHD	HYP.3	0.108	0.000	0.000
ADHD	EMO.4	-0.011	0.409	0.518
ADHD	PRO.4	-0.021	0.115	0.189
ADHD	COND.4	0.078	0.000	0.000
ADHD	PEER.4	0.045	0.001	0.002
ADHD	PRO.5	0.004	0.753	0.842
ADHD	HYP.4	0.080	0.000	0.000
ADHD	COND.5	0.040	0.003	0.006
ADHD	PEER.5	0.052	0.000	0.000
ADHD	EMO.5	0.007	0.587	0.676
ADHD	HYP.5	0.098	0.000	0.000
EA	DEP.1	0.000	0.979	0.979
EA	DEP.2	-0.044	0.001	0.002
EA	DEP.3	0.019	0.166	0.214
EA	DEP.4	-0.061	0.000	0.000
EA	DEP.5	-0.026	0.052	0.083
EA	DEP.6	-0.024	0.069	0.106
EA	DEP.7	-0.045	0.001	0.002
EA	DEP.8	-0.027	0.045	0.074
EA	DEP.9	-0.036	0.007	0.015

EA	DEP.10	0.004	0.794	0.888
EA	DEP.11	-0.047	0.001	0.002
EA	DEP.12	-0.043	0.001	0.003
EA	DEP.13	-0.021	0.121	0.165
EA	PRO.1	0.031	0.023	0.044
EA	HYP.1	-0.080	0.000	0.000
EA	EMO.1	-0.054	0.000	0.000
EA	PRO.2	0.001	0.947	0.973
EA	COND.1	-0.068	0.000	0.000
EA	PEER.1	0.044	0.001	0.003
EA	COND.2	-0.063	0.000	0.000
EA	EMO.2	0.019	0.169	0.214
EA	PRO.3	-0.027	0.044	0.074
EA	HYP.2	-0.039	0.004	0.008
EA	PEER.2	-0.027	0.043	0.074
EA	COND.3	-0.056	0.000	0.000
EA	EMO.3	0.003	0.835	0.907
EA	PEER.3	0.021	0.111	0.162
EA	HYP.3	-0.130	0.000	0.000
EA	EMO.4	-0.009	0.506	0.601
EA	PRO.4	-0.001	0.919	0.970
EA	COND.4	-0.085	0.000	0.000
EA	PEER.4	-0.013	0.353	0.433
EA	PRO.5	-0.051	0.000	0.001
EA	HYP.4	-0.101	0.000	0.000
EA	COND.5	-0.057	0.000	0.000
EA	PEER.5	-0.021	0.121	0.165
EA	EMO.5	-0.005	0.707	0.815
EA	HYP.5	-0.119	0.000	0.000
DEP	DEP.1	0.070	0.000	0.000
DEP	DEP.2	0.057	0.000	0.000
DEP	DEP.3	0.034	0.012	0.019
DEP	DEP.4	0.031	0.023	0.034
DEP	DEP.5	0.045	0.001	0.003
DEP	DEP.6	0.045	0.001	0.003
DEP	DEP.7	0.040	0.003	0.006
DEP	DEP.8	0.043	0.001	0.004
DEP	DEP.9	0.039	0.004	0.007
DEP	DEP.10	0.048	0.000	0.002
DEP	DEP.11	0.046	0.001	0.003
DEP	DEP.12	0.045	0.001	0.003
DEP	DEP.13	0.029	0.031	0.043

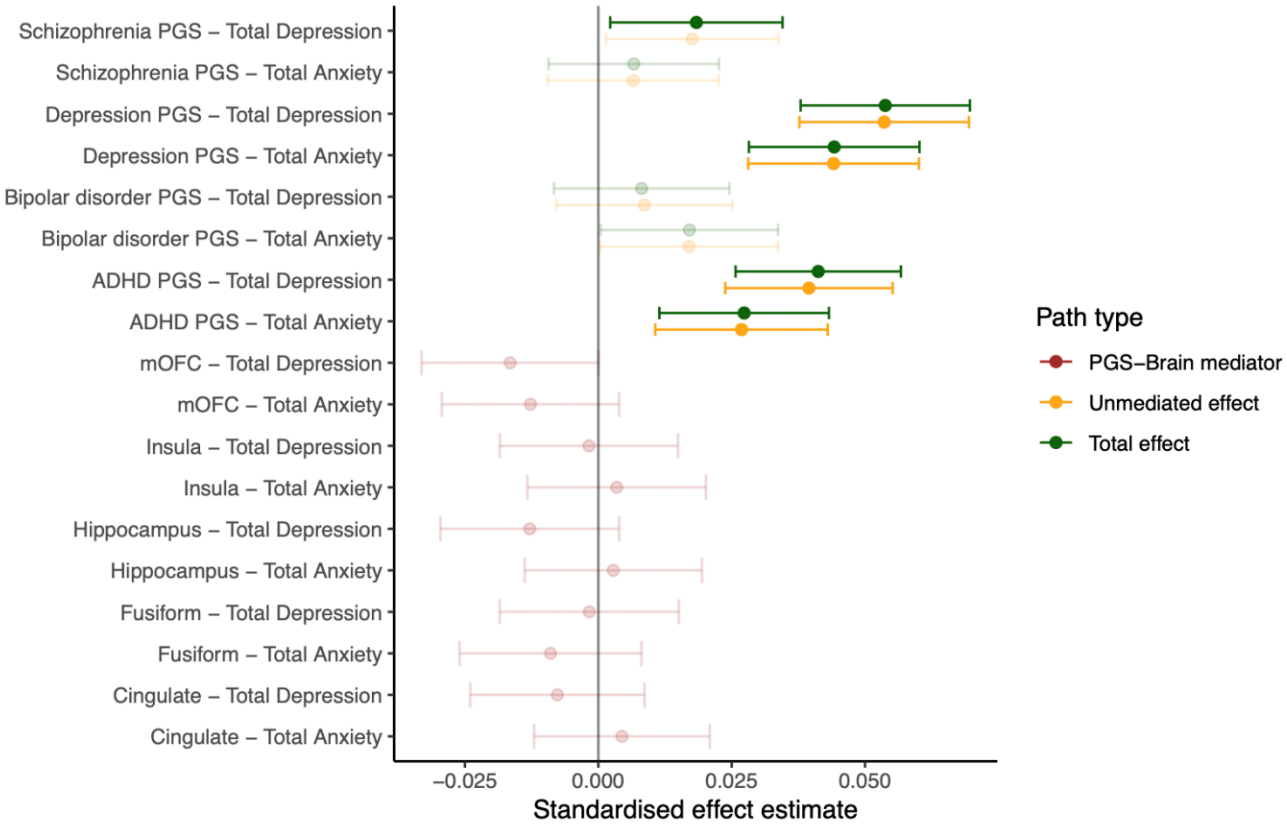
DEP	PRO.1	-0.027	0.047	0.059
DEP	HYP.1	0.029	0.032	0.043
DEP	EMO.1	0.044	0.001	0.003
DEP	PRO.2	-0.025	0.064	0.078
DEP	COND.1	0.054	0.000	0.000
DEP	PEER.1	0.034	0.010	0.018
DEP	COND.2	0.043	0.001	0.004
DEP	EMO.2	0.058	0.000	0.000
DEP	PRO.3	0.015	0.261	0.275
DEP	HYP.2	0.019	0.155	0.173
DEP	PEER.2	0.028	0.037	0.049
DEP	COND.3	0.007	0.604	0.604
DEP	EMO.3	0.047	0.001	0.003
DEP	PEER.3	0.040	0.003	0.007
DEP	HYP.3	0.041	0.002	0.006
DEP	EMO.4	0.016	0.245	0.266
DEP	PRO.4	-0.008	0.543	0.557
DEP	COND.4	0.041	0.002	0.005
DEP	PEER.4	0.074	0.000	0.000
DEP	PRO.5	0.021	0.122	0.140
DEP	HYP.4	0.035	0.009	0.017
DEP	COND.5	0.021	0.113	0.134
DEP	PEER.5	0.040	0.003	0.006
DEP	EMO.5	0.032	0.019	0.028
DEP	HYP.5	0.033	0.013	0.021
Yellow cells indicate adjusted p-values < 0.05				

Appendix B – Supplementary Material for Chapter 3

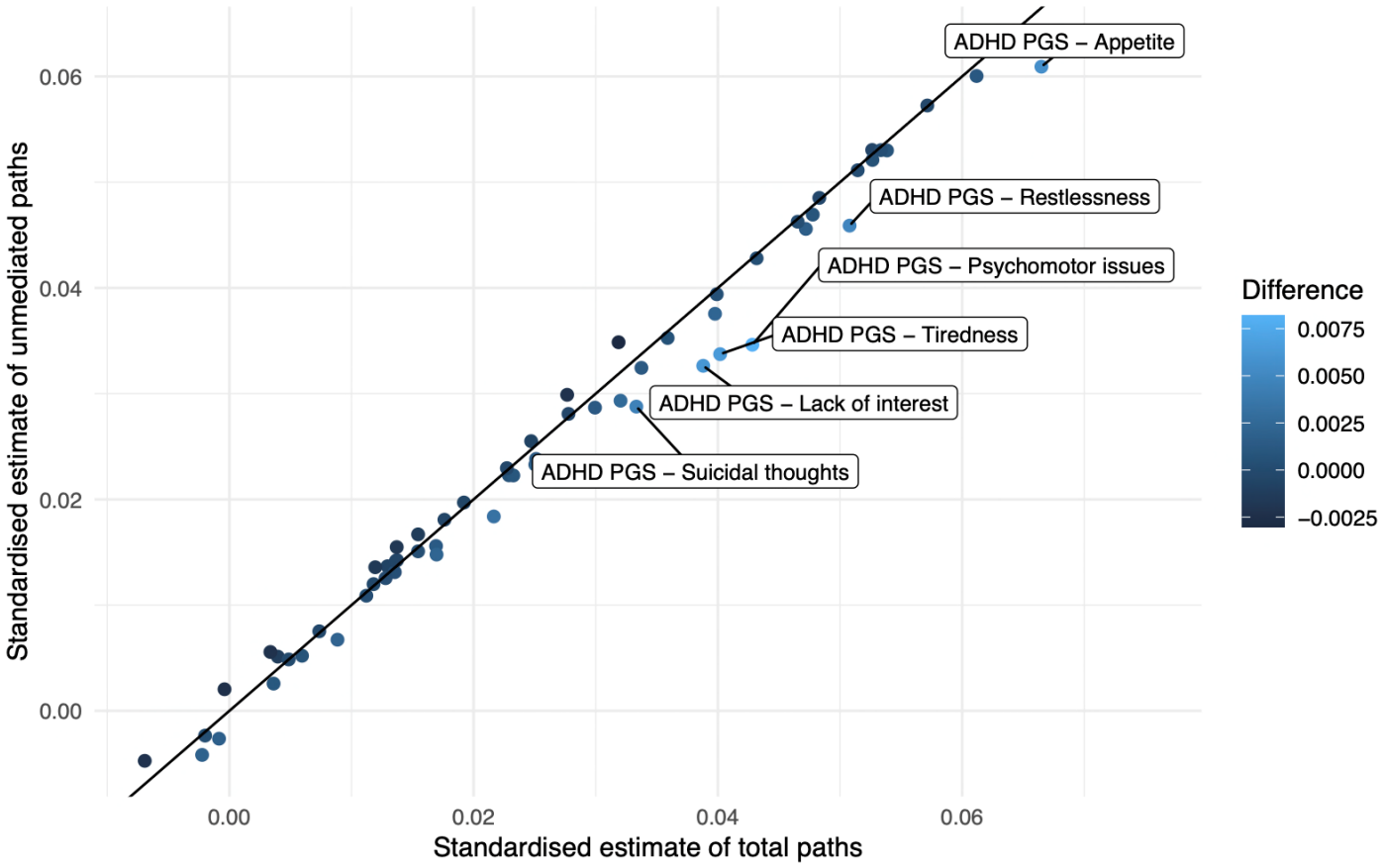
Supplementary Figures



Supplementary Figure 1: Standardised estimates of total mediation paths in 'Single PGS' (black) and 'Multiple PGSs' models (pink). Points are faded when non-significant according to FDR-corrected p-values.



Supplementary Figure 2: Standardised estimates of total (green) and unmediated (yellow) effects and associations between PGSs and brain mediators (brown) in the 'Total score' models. Points are faded when non-significant according to FDR-corrected p-values.



Supplementary Figure 3: Scatter plot of standardised estimates of total and unmediated paths in 'Multiple PGSs' model. Points are coloured according to the (non-significant) difference between total and unmediated estimates. Differences larger than 0.004 are labelled.

Supplementary Tables

Supplementary Table 1: 'Single PGS' and 'Multiple PGSs' mediation analysis results

Estimate	Lower CI	Upper CI	Path type	p-value	Adjusted p-value	Label	Model
-0.003	-0.030	0.023	b	0.798	0.916	mofc - anx	single
0.002	-0.025	0.029	b	0.861	0.940	fusi - anx	single
0.007	-0.020	0.034	b	0.609	0.809	ins - anx	single
-0.003	-0.029	0.024	b	0.853	0.940	hip - anx	single
0.008	-0.018	0.033	b	0.547	0.746	cing - anx	single
0.056	0.033	0.080	c	0.000	0.000	dep.pgs - anx	single
-0.016	-0.043	0.011	b	0.255	0.476	mofc - wor	single
-0.019	-0.047	0.009	b	0.187	0.390	fusi - wor	single
-0.003	-0.032	0.025	b	0.816	0.919	ins - wor	single
0.005	-0.023	0.033	b	0.724	0.884	hip - wor	single
-0.002	-0.028	0.025	b	0.905	0.972	cing - wor	single
0.057	0.033	0.082	c	0.000	0.000	dep.pgs - wor	single
-0.052	-0.095	-0.008	b	0.020	0.070	mofc - psy	single
-0.043	-0.089	0.002	b	0.063	0.163	fusi - psy	single
-0.039	-0.084	0.007	b	0.097	0.233	ins - psy	single
-0.027	-0.071	0.017	b	0.234	0.464	hip - psy	single
-0.039	-0.081	0.003	b	0.067	0.168	cing - psy	single
0.067	0.027	0.107	c	0.001	0.007	dep.pgs - psy	single
-0.012	-0.040	0.016	b	0.389	0.634	mofc - dep	single
-0.011	-0.039	0.018	b	0.472	0.687	fusi - dep	single
-0.006	-0.035	0.023	b	0.699	0.881	ins - dep	single
-0.021	-0.049	0.008	b	0.158	0.340	hip - dep	single
-0.002	-0.029	0.024	b	0.866	0.940	cing - dep	single
0.073	0.049	0.098	c	0.000	0.000	dep.pgs - dep	single
-0.009	-0.039	0.020	b	0.531	0.745	mofc - ina	single
-0.022	-0.052	0.008	b	0.146	0.321	fusi - ina	single
-0.013	-0.043	0.017	b	0.387	0.634	ins - ina	single
-0.035	-0.066	-0.005	b	0.021	0.072	hip - ina	single
-0.011	-0.039	0.017	b	0.451	0.680	cing - ina	single
0.050	0.024	0.077	c	0.000	0.001	dep.pgs - ina	single
-0.040	-0.063	-0.016	b	0.001	0.006	mofc - tir	single
-0.027	-0.051	-0.003	b	0.028	0.083	fusi - tir	single
-0.034	-0.058	-0.010	b	0.005	0.027	ins - tir	single
-0.022	-0.046	0.002	b	0.068	0.168	hip - tir	single
-0.033	-0.055	-0.010	b	0.005	0.027	cing - tir	single
0.075	0.054	0.096	c	0.000	0.000	dep.pgs - tir	single
-0.031	-0.059	-0.002	b	0.036	0.104	mofc - int	single

-0.037	-0.067	-0.008	b	0.013	0.052	fusi - int	single
-0.025	-0.054	0.005	b	0.105	0.247	ins - int	single
-0.033	-0.063	-0.004	b	0.024	0.080	hip - int	single
-0.030	-0.057	-0.002	b	0.037	0.104	cing - int	single
0.071	0.046	0.097	c	0.000	0.000	dep.pgs - int	single
-0.038	-0.067	-0.008	b	0.012	0.048	mofc - app	single
-0.005	-0.035	0.025	b	0.746	0.890	fusi - app	single
-0.034	-0.065	-0.004	b	0.028	0.083	ins - app	single
-0.034	-0.064	-0.004	b	0.026	0.082	hip - app	single
-0.034	-0.062	-0.005	b	0.020	0.070	cing - app	single
0.075	0.048	0.101	c	0.000	0.000	dep.pgs - app	single
-0.002	-0.049	0.045	b	0.935	0.976	mofc - sui	single
-0.033	-0.082	0.016	b	0.189	0.390	fusi - sui	single
-0.020	-0.069	0.029	b	0.414	0.664	ins - sui	single
-0.071	-0.122	-0.021	b	0.006	0.027	hip - sui	single
-0.007	-0.052	0.039	b	0.773	0.907	cing - sui	single
0.062	0.019	0.105	c	0.005	0.027	dep.pgs - sui	single
0.008	-0.021	0.037	b	0.591	0.795	mofc - con	single
-0.001	-0.030	0.028	b	0.947	0.976	fusi - con	single
0.013	-0.016	0.042	b	0.386	0.634	ins - con	single
0.003	-0.026	0.032	b	0.819	0.919	hip - con	single
0.015	-0.012	0.043	b	0.272	0.499	cing - con	single
0.071	0.045	0.096	c	0.000	0.000	dep.pgs - con	single
-0.022	-0.045	0.001	b	0.057	0.156	mofc - sle	single
-0.005	-0.029	0.018	b	0.653	0.856	fusi - sle	single
-0.014	-0.037	0.010	b	0.251	0.476	ins - sle	single
-0.001	-0.025	0.022	b	0.920	0.976	hip - sle	single
-0.028	-0.050	-0.006	b	0.014	0.052	cing - sle	single
0.046	0.025	0.066	c	0.000	0.000	dep.pgs - sle	single
-0.016	-0.043	0.011	b	0.239	0.464	mofc - irr	single
-0.001	-0.029	0.027	b	0.945	0.976	fusi - irr	single
-0.011	-0.039	0.016	b	0.421	0.665	ins - irr	single
0.009	-0.019	0.036	b	0.541	0.746	hip - irr	single
-0.011	-0.037	0.016	b	0.429	0.667	cing - irr	single
0.063	0.038	0.087	c	0.000	0.000	dep.pgs - irr	single
-0.006	-0.036	0.024	b	0.694	0.881	mofc - fore	single
-0.004	-0.035	0.026	b	0.781	0.907	fusi - fore	single
0.000	-0.031	0.030	b	0.979	0.985	ins - fore	single
-0.001	-0.031	0.030	b	0.964	0.983	hip - fore	single
0.015	-0.014	0.044	b	0.308	0.537	cing - fore	single
0.067	0.041	0.093	c	0.000	0.000	dep.pgs - fore	single
-0.022	-0.056	0.012	b	0.200	0.403	mofc - res	single

-0.026	-0.061	0.009	b	0.146	0.321	fusi - res	single
-0.020	-0.055	0.016	b	0.282	0.509	ins - res	single
-0.034	-0.069	0.002	b	0.062	0.163	hip - res	single
-0.027	-0.060	0.007	b	0.117	0.269	cing - res	single
0.062	0.031	0.093	c	0.000	0.001	dep.pgs - res	single
-0.010	-0.036	0.016	b	0.465	0.687	mofc - rel	single
-0.011	-0.038	0.016	b	0.442	0.677	fusi - rel	single
-0.005	-0.032	0.022	b	0.727	0.884	ins - rel	single
0.000	-0.027	0.027	b	0.985	0.985	hip - rel	single
-0.009	-0.034	0.017	b	0.512	0.728	cing - rel	single
0.064	0.040	0.087	c	0.000	0.000	dep.pgs - rel	single
-0.005	-0.030	0.020	b	0.695	0.881	mofc - wor.t	single
-0.012	-0.038	0.014	b	0.376	0.634	fusi - wor.t	single
-0.004	-0.030	0.022	b	0.749	0.890	ins - wor.t	single
0.009	-0.017	0.036	b	0.476	0.687	hip - wor.t	single
-0.005	-0.029	0.020	b	0.706	0.881	cing - wor.t	single
0.058	0.035	0.081	c	0.000	0.000	dep.pgs - wor.t	single
-0.022	-0.038	-0.006	a	0.008	0.037	dep.pgs - mofc	single
-0.022	-0.038	-0.007	a	0.005	0.027	dep.pgs - fusi	single
-0.022	-0.038	-0.006	a	0.007	0.032	dep.pgs - ins	single
-0.008	-0.024	0.008	a	0.308	0.537	dep.pgs - hip	single
-0.022	-0.038	-0.005	a	0.011	0.044	dep.pgs - cing	single
0.056	0.032	0.080	t	0.000	0.000	dep.pgs - anx	single
0.058	0.034	0.083	t	0.000	0.000	dep.pgs - wor	single
0.071	0.031	0.111	t	0.000	0.001	dep.pgs - psy	single
0.074	0.050	0.099	t	0.000	0.000	dep.pgs - dep	single
0.052	0.026	0.078	t	0.000	0.000	dep.pgs - ina	single
0.079	0.058	0.100	t	0.000	0.000	dep.pgs - tir	single
0.074	0.049	0.099	t	0.000	0.000	dep.pgs - int	single
0.077	0.051	0.104	t	0.000	0.000	dep.pgs - app	single
0.064	0.021	0.107	t	0.003	0.003	dep.pgs - sui	single
0.070	0.044	0.095	t	0.000	0.000	dep.pgs - con	single
0.047	0.026	0.068	t	0.000	0.000	dep.pgs - sle	single
0.063	0.039	0.088	t	0.000	0.000	dep.pgs - irr	single
0.067	0.041	0.093	t	0.000	0.000	dep.pgs - fore	single
0.065	0.034	0.095	t	0.000	0.000	dep.pgs - res	single
0.065	0.041	0.088	t	0.000	0.000	dep.pgs - rel	single
0.059	0.036	0.082	t	0.000	0.000	dep.pgs - wor.t	single
0.000	-0.002	0.002	m tot	0.775	0.826	dep.pgs - anx	single
0.001	-0.001	0.003	m tot	0.433	0.583	dep.pgs - wor	single
0.004	0.000	0.008	m tot	0.054	0.240	dep.pgs - psy	single
0.001	-0.001	0.003	m tot	0.440	0.583	dep.pgs - dep	single

0.002	-0.001	0.004	m tot	0.218	0.499	dep.pgs - ina	single
0.003	0.001	0.006	m tot	0.018	0.240	dep.pgs - tir	single
0.003	0.000	0.006	m tot	0.040	0.240	dep.pgs - int	single
0.003	0.000	0.006	m tot	0.060	0.240	dep.pgs - app	single
0.002	-0.002	0.006	m tot	0.322	0.583	dep.pgs - sui	single
-0.001	-0.003	0.001	m tot	0.473	0.583	dep.pgs - con	single
0.002	0.000	0.003	m tot	0.124	0.331	dep.pgs - sle	single
0.001	-0.001	0.003	m tot	0.452	0.583	dep.pgs - irr	single
0.000	-0.002	0.002	m tot	0.942	0.942	dep.pgs - fore	single
0.002	-0.001	0.005	m tot	0.121	0.331	dep.pgs - res	single
0.001	-0.001	0.003	m tot	0.468	0.583	dep.pgs - rel	single
0.000	-0.001	0.002	m tot	0.613	0.701	dep.pgs - wor.t	single
0.000	-0.001	0.001	m	0.799	0.954	dep.pgs - mofc - anx	single
0.000	0.000	0.001	m	0.296	0.810	dep.pgs - mofc - wor	single
0.001	0.000	0.002	m	0.081	0.703	dep.pgs - mofc - psy	single
0.000	0.000	0.001	m	0.413	0.810	dep.pgs - mofc - dep	single
0.000	0.000	0.001	m	0.542	0.860	dep.pgs - mofc - ina	single
0.001	0.000	0.002	m	0.039	0.703	dep.pgs - mofc - tir	single
0.001	0.000	0.001	m	0.101	0.703	dep.pgs - mofc - int	single
0.001	0.000	0.002	m	0.069	0.703	dep.pgs - mofc - app	single
0.000	-0.001	0.001	m	0.935	1.000	dep.pgs - mofc - sui	single
0.000	-0.001	0.000	m	0.598	0.889	dep.pgs - mofc - 0	single
0.000	0.000	0.001	m	0.123	0.703	dep.pgs - mofc - anx	single
0.000	0.000	0.001	m	0.282	0.810	dep.pgs - mofc - wor	single
0.000	-0.001	0.001	m	0.697	0.938	dep.pgs - mofc - psy	single
0.000	0.000	0.001	m	0.249	0.810	dep.pgs - mofc - dep	single
0.000	0.000	0.001	m	0.481	0.810	dep.pgs - mofc - ina	single
0.000	0.000	0.001	m	0.698	0.938	dep.pgs - mofc - tir	single
0.000	-0.001	0.001	m	0.861	0.976	dep.pgs - fusi - anx	single
0.000	0.000	0.001	m	0.234	0.810	dep.pgs - fusi - wor	single
0.001	0.000	0.002	m	0.122	0.703	dep.pgs - fusi - psy	single
0.000	0.000	0.001	m	0.486	0.810	dep.pgs - fusi - dep	single
0.000	0.000	0.001	m	0.198	0.791	dep.pgs - fusi - ina	single
0.001	0.000	0.001	m	0.085	0.703	dep.pgs - fusi - tir	single
0.001	0.000	0.002	m	0.065	0.703	dep.pgs - fusi - int	single
0.000	-0.001	0.001	m	0.748	0.938	dep.pgs - fusi - app	single
0.001	0.000	0.002	m	0.235	0.810	dep.pgs - fusi - sui	single
0.000	-0.001	0.001	m	0.947	1.000	dep.pgs - fusi - 0	single
0.000	0.000	0.001	m	0.657	0.938	dep.pgs - fusi - anx	single
0.000	-0.001	0.001	m	0.945	1.000	dep.pgs - fusi - wor	single
0.000	-0.001	0.001	m	0.782	0.948	dep.pgs - fusi - psy	single
0.001	0.000	0.001	m	0.197	0.791	dep.pgs - fusi - dep	single

0.000	0.000	0.001	m	0.459	0.810	dep.pgs - fusi - ina	single
0.000	0.000	0.001	m	0.399	0.810	dep.pgs - fusi - tir	single
0.000	-0.001	0.000	m	0.615	0.894	dep.pgs - ins - anx	single
0.000	-0.001	0.001	m	0.816	0.955	dep.pgs - ins - wor	single
0.001	0.000	0.002	m	0.157	0.775	dep.pgs - ins - psy	single
0.000	-0.001	0.001	m	0.702	0.938	dep.pgs - ins - dep	single
0.000	0.000	0.001	m	0.410	0.810	dep.pgs - ins - ina	single
0.001	0.000	0.002	m	0.052	0.703	dep.pgs - ins - tir	single
0.001	0.000	0.001	m	0.165	0.775	dep.pgs - ins - int	single
0.001	0.000	0.002	m	0.088	0.703	dep.pgs - ins - app	single
0.000	-0.001	0.002	m	0.434	0.810	dep.pgs - ins - sui	single
0.000	-0.001	0.000	m	0.409	0.810	dep.pgs - ins - 0	single
0.000	0.000	0.001	m	0.291	0.810	dep.pgs - ins - anx	single
0.000	0.000	0.001	m	0.441	0.810	dep.pgs - ins - wor	single
0.000	-0.001	0.001	m	0.979	1.000	dep.pgs - ins - psy	single
0.000	0.000	0.001	m	0.318	0.810	dep.pgs - ins - dep	single
0.000	-0.001	0.001	m	0.729	0.938	dep.pgs - ins - ina	single
0.000	0.000	0.001	m	0.751	0.938	dep.pgs - ins - tir	single
0.000	0.000	0.000	m	NA	NA	dep.pgs - hip - anx	single
0.000	0.000	0.000	m	0.739	0.938	dep.pgs - hip - wor	single
0.000	0.000	0.001	m	0.439	0.810	dep.pgs - hip - psy	single
0.000	0.000	0.001	m	0.409	0.810	dep.pgs - hip - dep	single
0.000	0.000	0.001	m	0.352	0.810	dep.pgs - hip - ina	single
0.000	0.000	0.001	m	0.374	0.810	dep.pgs - hip - tir	single
0.000	0.000	0.001	m	0.353	0.810	dep.pgs - hip - int	single
0.000	0.000	0.001	m	0.354	0.810	dep.pgs - hip - app	single
0.001	-0.001	0.002	m	0.339	0.810	dep.pgs - hip - sui	single
0.000	0.000	0.000	m	0.823	0.955	dep.pgs - hip - 0	single
0.000	0.000	0.000	m	NA	NA	dep.pgs - hip - anx	single
0.000	0.000	0.000	m	0.600	0.889	dep.pgs - hip - wor	single
0.000	0.000	0.000	m	0.964	1.000	dep.pgs - hip - psy	single
0.000	0.000	0.001	m	0.371	0.810	dep.pgs - hip - dep	single
0.000	0.000	0.000	m	NA	NA	dep.pgs - hip - ina	single
0.000	0.000	0.000	m	0.559	0.860	dep.pgs - hip - tir	single
0.000	-0.001	0.000	m	0.558	0.860	dep.pgs - cing - anx	single
0.000	-0.001	0.001	m	0.905	1.000	dep.pgs - cing - wor	single
0.001	0.000	0.002	m	0.137	0.729	dep.pgs - cing - psy	single
0.000	-0.001	0.001	m	0.866	0.976	dep.pgs - cing - dep	single
0.000	0.000	0.001	m	0.470	0.810	dep.pgs - cing - ina	single
0.001	0.000	0.001	m	0.058	0.703	dep.pgs - cing - tir	single
0.001	0.000	0.001	m	0.106	0.703	dep.pgs - cing - int	single
0.001	0.000	0.002	m	0.085	0.703	dep.pgs - cing - app	single

0.000	-0.001	0.001	m	0.775	0.948	dep.pgs - cing - sui	single
0.000	-0.001	0.000	m	0.312	0.810	dep.pgs - cing - 0	single
0.001	0.000	0.001	m	0.076	0.703	dep.pgs - cing - anx	single
0.000	0.000	0.001	m	0.450	0.810	dep.pgs - cing - wor	single
0.000	-0.001	0.000	m	0.344	0.810	dep.pgs - cing - psy	single
0.001	0.000	0.001	m	0.181	0.791	dep.pgs - cing - dep	single
0.000	0.000	0.001	m	0.525	0.857	dep.pgs - cing - ina	single
0.000	0.000	0.001	m	0.709	0.938	dep.pgs - cing - tir	single
-0.002	-0.026	0.022	b	0.845	0.959	mofc - anx	single
0.003	-0.022	0.027	b	0.825	0.958	fusi - anx	single
0.008	-0.016	0.033	b	0.504	0.679	ins - anx	single
-0.002	-0.026	0.022	b	0.868	0.974	hip - anx	single
0.009	-0.015	0.032	b	0.466	0.661	cing - anx	single
0.030	0.008	0.051	c	0.008	0.035	adhd.pgs - anx	single
-0.014	-0.039	0.011	b	0.262	0.465	mofc - wor	single
-0.018	-0.043	0.007	b	0.161	0.324	fusi - wor	single
-0.002	-0.028	0.024	b	0.892	0.979	ins - wor	single
0.005	-0.020	0.031	b	0.673	0.872	hip - wor	single
0.000	-0.024	0.024	b	0.982	0.992	cing - wor	single
0.040	0.018	0.063	c	0.000	0.003	adhd.pgs - wor	single
-0.049	-0.089	-0.009	b	0.016	0.055	mofc - psy	single
-0.041	-0.083	0.000	b	0.051	0.130	fusi - psy	single
-0.036	-0.078	0.005	b	0.089	0.208	ins - psy	single
-0.025	-0.066	0.015	b	0.216	0.413	hip - psy	single
-0.037	-0.075	0.001	b	0.058	0.139	cing - psy	single
0.053	0.017	0.090	c	0.004	0.020	adhd.pgs - psy	single
-0.011	-0.036	0.014	b	0.397	0.636	mofc - dep	single
-0.010	-0.036	0.016	b	0.464	0.661	fusi - dep	single
-0.005	-0.031	0.022	b	0.730	0.911	ins - dep	single
-0.019	-0.045	0.007	b	0.143	0.302	hip - dep	single
-0.002	-0.026	0.023	b	0.888	0.979	cing - dep	single
0.043	0.020	0.066	c	0.000	0.002	adhd.pgs - dep	single
-0.008	-0.035	0.019	b	0.557	0.740	mofc - ina	single
-0.021	-0.049	0.006	b	0.124	0.271	fusi - ina	single
-0.012	-0.040	0.015	b	0.381	0.631	ins - ina	single
-0.034	-0.061	-0.006	b	0.016	0.055	hip - ina	single
-0.010	-0.036	0.016	b	0.452	0.661	cing - ina	single
0.033	0.008	0.058	c	0.009	0.035	adhd.pgs - ina	single
-0.038	-0.059	-0.017	b	0.000	0.003	mofc - tir	single
-0.026	-0.048	-0.004	b	0.021	0.065	fusi - tir	single
-0.032	-0.054	-0.010	b	0.004	0.019	ins - tir	single
-0.021	-0.042	0.001	b	0.058	0.139	hip - tir	single

-0.031	-0.052	-0.010	b	0.003	0.017	cing - tir	single
0.053	0.033	0.072	c	0.000	0.000	adhd.pgs - tir	single
-0.029	-0.055	-0.003	b	0.030	0.086	mofc - int	single
-0.036	-0.063	-0.009	b	0.009	0.035	fusi - int	single
-0.023	-0.050	0.004	b	0.101	0.232	ins - int	single
-0.032	-0.059	-0.006	b	0.016	0.055	hip - int	single
-0.028	-0.053	-0.003	b	0.031	0.086	cing - int	single
0.050	0.026	0.074	c	0.000	0.000	adhd.pgs - int	single
-0.034	-0.061	-0.007	b	0.014	0.052	mofc - app	single
-0.001	-0.029	0.026	b	0.917	0.984	fusi - app	single
-0.030	-0.058	-0.002	b	0.035	0.096	ins - app	single
-0.031	-0.059	-0.004	b	0.024	0.075	hip - app	single
-0.031	-0.057	-0.005	b	0.019	0.063	cing - app	single
0.079	0.054	0.103	c	0.000	0.000	adhd.pgs - app	single
-0.001	-0.044	0.042	b	0.964	0.984	mofc - sui	single
-0.033	-0.078	0.012	b	0.153	0.316	fusi - sui	single
-0.019	-0.063	0.026	b	0.409	0.636	ins - sui	single
-0.070	-0.116	-0.024	b	0.003	0.015	hip - sui	single
-0.006	-0.047	0.036	b	0.788	0.936	cing - sui	single
0.045	0.005	0.085	c	0.028	0.083	adhd.pgs - sui	single
0.010	-0.017	0.036	b	0.471	0.661	mofc - con	single
0.001	-0.025	0.028	b	0.926	0.984	fusi - con	single
0.015	-0.012	0.042	b	0.274	0.476	ins - con	single
0.005	-0.021	0.032	b	0.686	0.877	hip - con	single
0.017	-0.008	0.042	b	0.192	0.379	cing - con	single
0.049	0.026	0.073	c	0.000	0.000	adhd.pgs - con	single
-0.021	-0.042	0.000	b	0.045	0.117	mofc - sle	single
-0.005	-0.026	0.017	b	0.659	0.864	fusi - sle	single
-0.013	-0.034	0.009	b	0.244	0.440	ins - sle	single
-0.001	-0.022	0.021	b	0.944	0.984	hip - sle	single
-0.027	-0.047	-0.007	b	0.009	0.035	cing - sle	single
0.035	0.016	0.054	c	0.000	0.003	adhd.pgs - sle	single
-0.015	-0.039	0.010	b	0.243	0.440	mofc - irr	single
0.001	-0.025	0.026	b	0.963	0.984	fusi - irr	single
-0.009	-0.035	0.016	b	0.464	0.661	ins - irr	single
0.009	-0.016	0.034	b	0.480	0.664	hip - irr	single
-0.009	-0.033	0.015	b	0.454	0.661	cing - irr	single
0.047	0.025	0.070	c	0.000	0.000	adhd.pgs - irr	single
-0.005	-0.032	0.022	b	0.720	0.909	mofc - fore	single
-0.003	-0.031	0.025	b	0.835	0.958	fusi - fore	single
0.001	-0.027	0.029	b	0.961	0.984	ins - fore	single
-0.001	-0.029	0.027	b	0.955	0.984	hip - fore	single

0.016	-0.011	0.042	b	0.241	0.440	cing - fore	single
0.037	0.013	0.062	c	0.003	0.015	adhd.pgs - fore	single
-0.020	-0.052	0.011	b	0.200	0.389	mofc - res	single
-0.025	-0.056	0.007	b	0.126	0.271	fusi - res	single
-0.017	-0.049	0.016	b	0.314	0.538	ins - res	single
-0.033	-0.065	-0.001	b	0.045	0.117	hip - res	single
-0.025	-0.055	0.005	b	0.108	0.242	cing - res	single
0.060	0.032	0.088	c	0.000	0.000	adhd.pgs - res	single
-0.009	-0.033	0.014	b	0.437	0.661	mofc - rel	single
-0.010	-0.035	0.014	b	0.405	0.636	fusi - rel	single
-0.004	-0.029	0.021	b	0.764	0.919	ins - rel	single
0.000	-0.025	0.024	b	0.993	0.993	hip - rel	single
-0.008	-0.031	0.015	b	0.495	0.675	cing - rel	single
0.034	0.012	0.056	c	0.003	0.015	adhd.pgs - rel	single
-0.004	-0.027	0.019	b	0.757	0.919	mofc - wor.t	single
-0.012	-0.035	0.012	b	0.340	0.573	fusi - wor.t	single
-0.003	-0.027	0.021	b	0.811	0.953	ins - wor.t	single
0.010	-0.014	0.034	b	0.409	0.636	hip - wor.t	single
-0.004	-0.026	0.019	b	0.751	0.919	cing - wor.t	single
0.038	0.017	0.059	c	0.000	0.003	adhd.pgs - wor.t	single
-0.053	-0.068	-0.038	a	0.000	0.000	adhd.pgs - mofc	single
-0.041	-0.055	-0.027	a	0.000	0.000	adhd.pgs - fusi	single
-0.051	-0.066	-0.037	a	0.000	0.000	adhd.pgs - ins	single
-0.032	-0.047	-0.018	a	0.000	0.000	adhd.pgs - hip	single
-0.051	-0.066	-0.036	a	0.000	0.000	adhd.pgs - cing	single
0.029	0.007	0.050	t	0.009	0.009	adhd.pgs - anx	single
0.042	0.020	0.064	t	0.000	0.000	adhd.pgs - wor	single
0.062	0.026	0.098	t	0.001	0.001	adhd.pgs - psy	single
0.045	0.022	0.067	t	0.000	0.000	adhd.pgs - dep	single
0.037	0.012	0.061	t	0.003	0.004	adhd.pgs - ina	single
0.060	0.041	0.079	t	0.000	0.000	adhd.pgs - tir	single
0.057	0.033	0.080	t	0.000	0.000	adhd.pgs - int	single
0.085	0.061	0.109	t	0.000	0.000	adhd.pgs - app	single
0.050	0.010	0.089	t	0.013	0.013	adhd.pgs - sui	single
0.047	0.024	0.070	t	0.000	0.000	adhd.pgs - con	single
0.038	0.019	0.057	t	0.000	0.000	adhd.pgs - sle	single
0.049	0.027	0.071	t	0.000	0.000	adhd.pgs - irr	single
0.037	0.013	0.061	t	0.003	0.003	adhd.pgs - fore	single
0.065	0.038	0.093	t	0.000	0.000	adhd.pgs - res	single
0.035	0.014	0.057	t	0.001	0.002	adhd.pgs - rel	single
0.039	0.018	0.059	t	0.000	0.000	adhd.pgs - wor.t	single
-0.001	-0.005	0.003	m tot	0.708	0.793	adhd.pgs - anx	single

0.001	-0.003	0.006	m tot	0.520	0.640	adhd.pgs - wor	single
0.009	0.002	0.016	m tot	0.018	0.070	adhd.pgs - psy	single
0.002	-0.002	0.006	m tot	0.392	0.627	adhd.pgs - dep	single
0.004	-0.001	0.008	m tot	0.142	0.324	adhd.pgs - ina	single
0.007	0.003	0.011	m tot	0.001	0.011	adhd.pgs - tir	single
0.007	0.002	0.011	m tot	0.007	0.054	adhd.pgs - int	single
0.006	0.001	0.011	m tot	0.016	0.070	adhd.pgs - app	single
0.005	-0.003	0.013	m tot	0.209	0.417	adhd.pgs - sui	single
-0.002	-0.007	0.002	m tot	0.312	0.555	adhd.pgs - con	single
0.003	0.000	0.007	m tot	0.074	0.197	adhd.pgs - sle	single
0.001	-0.003	0.006	m tot	0.517	0.640	adhd.pgs - irr	single
0.000	-0.005	0.004	m tot	0.858	0.858	adhd.pgs - fore	single
0.005	0.000	0.011	m tot	0.065	0.197	adhd.pgs - res	single
0.002	-0.003	0.006	m tot	0.473	0.640	adhd.pgs - rel	single
0.001	-0.003	0.005	m tot	0.743	0.793	adhd.pgs - wor.t	single
0.000	-0.001	0.001	m	0.845	0.989	adhd.pgs - mofc - anx	single
0.001	-0.001	0.002	m	0.268	0.596	adhd.pgs - mofc - wor	single
0.003	0.000	0.005	m	0.022	0.222	adhd.pgs - mofc - psy	single
0.001	-0.001	0.002	m	0.401	0.743	adhd.pgs - mofc - dep	single
0.000	-0.001	0.002	m	0.558	0.812	adhd.pgs - mofc - ina	single
0.002	0.001	0.003	m	0.002	0.139	adhd.pgs - mofc - tir	single
0.002	0.000	0.003	m	0.038	0.225	adhd.pgs - mofc - int	single
0.002	0.000	0.003	m	0.020	0.222	adhd.pgs - mofc - app	single
0.000	-0.002	0.002	m	0.964	0.989	adhd.pgs - mofc - sui	single
-0.001	-0.002	0.001	m	0.474	0.743	adhd.pgs - mofc - 0	single
0.001	0.000	0.002	m	0.054	0.254	adhd.pgs - mofc - anx	single
0.001	-0.001	0.002	m	0.249	0.572	adhd.pgs - mofc - wor	single
0.000	-0.001	0.002	m	0.720	0.971	adhd.pgs - mofc - psy	single
0.001	-0.001	0.003	m	0.208	0.536	adhd.pgs - mofc - dep	single
0.001	-0.001	0.002	m	0.440	0.743	adhd.pgs - mofc - ina	single
0.000	-0.001	0.001	m	0.757	0.971	adhd.pgs - mofc - tir	single
0.000	-0.001	0.001	m	0.825	0.989	adhd.pgs - fusi - anx	single
0.001	0.000	0.002	m	0.173	0.478	adhd.pgs - fusi - wor	single
0.002	0.000	0.003	m	0.066	0.272	adhd.pgs - fusi - psy	single
0.000	-0.001	0.001	m	0.468	0.743	adhd.pgs - fusi - dep	single
0.001	0.000	0.002	m	0.138	0.430	adhd.pgs - fusi - ina	single
0.001	0.000	0.002	m	0.032	0.225	adhd.pgs - fusi - tir	single
0.001	0.000	0.003	m	0.018	0.222	adhd.pgs - fusi - int	single
0.000	-0.001	0.001	m	0.917	0.989	adhd.pgs - fusi - app	single
0.001	-0.001	0.003	m	0.166	0.475	adhd.pgs - fusi - sui	single

0.000	-0.001	0.001	m	0.926	0.989	adhd.pgs - fusi - 0	single
0.000	-0.001	0.001	m	0.660	0.943	adhd.pgs - fusi - anx	single
0.000	-0.001	0.001	m	0.963	0.989	adhd.pgs - fusi - wor	single
0.000	-0.001	0.001	m	0.835	0.989	adhd.pgs - fusi - psy	single
0.001	0.000	0.002	m	0.140	0.430	adhd.pgs - fusi - dep	single
0.000	-0.001	0.001	m	0.410	0.743	adhd.pgs - fusi - ina	single
0.000	-0.001	0.001	m	0.347	0.712	adhd.pgs - fusi - tir	single
0.000	-0.002	0.001	m	0.506	0.750	adhd.pgs - ins - anx	single
0.000	-0.001	0.001	m	0.892	0.989	adhd.pgs - ins - wor	single
0.002	0.000	0.004	m	0.098	0.358	adhd.pgs - ins - psy	single
0.000	-0.001	0.002	m	0.731	0.971	adhd.pgs - ins - dep	single
0.001	-0.001	0.002	m	0.385	0.743	adhd.pgs - ins - ina	single
0.002	0.000	0.003	m	0.008	0.205	adhd.pgs - ins - tir	single
0.001	0.000	0.003	m	0.111	0.385	adhd.pgs - ins - int	single
0.002	0.000	0.003	m	0.044	0.225	adhd.pgs - ins - app	single
0.001	-0.001	0.003	m	0.412	0.743	adhd.pgs - ins - sui	single
-0.001	-0.002	0.001	m	0.280	0.604	adhd.pgs - ins - 0	single
0.001	0.000	0.002	m	0.250	0.572	adhd.pgs - ins - anx	single
0.000	-0.001	0.002	m	0.466	0.743	adhd.pgs - ins - wor	single
0.000	-0.001	0.001	m	0.961	0.989	adhd.pgs - ins - psy	single
0.001	-0.001	0.003	m	0.319	0.672	adhd.pgs - ins - dep	single
0.000	-0.001	0.001	m	0.765	0.971	adhd.pgs - ins - ina	single
0.000	-0.001	0.001	m	0.811	0.989	adhd.pgs - ins - tir	single
0.000	-0.001	0.001	m	0.868	0.989	adhd.pgs - hip - anx	single
0.000	-0.001	0.001	m	0.674	0.947	adhd.pgs - hip - wor	single
0.001	-0.001	0.002	m	0.234	0.572	adhd.pgs - hip - psy	single
0.001	0.000	0.002	m	0.165	0.475	adhd.pgs - hip - dep	single
0.001	0.000	0.002	m	0.034	0.225	adhd.pgs - hip - ina	single
0.001	0.000	0.001	m	0.081	0.310	adhd.pgs - hip - tir	single
0.001	0.000	0.002	m	0.035	0.225	adhd.pgs - hip - int	single
0.001	0.000	0.002	m	0.045	0.225	adhd.pgs - hip - app	single
0.002	0.000	0.004	m	0.013	0.222	adhd.pgs - hip - sui	single
0.000	-0.001	0.001	m	0.687	0.948	adhd.pgs - hip - 0	single
0.000	-0.001	0.001	m	0.944	0.989	adhd.pgs - hip - anx	single
0.000	-0.001	0.001	m	0.486	0.747	adhd.pgs - hip - wor	single
0.000	-0.001	0.001	m	0.955	0.989	adhd.pgs - hip - psy	single
0.001	0.000	0.002	m	0.068	0.272	adhd.pgs - hip - dep	single
0.000	-0.001	0.001	m	0.993	0.993	adhd.pgs - hip - ina	single
0.000	-0.001	0.000	m	0.417	0.743	adhd.pgs - hip - tir	single
0.000	-0.002	0.001	m	0.468	0.743	adhd.pgs - cing - anx	single
0.000	-0.001	0.001	m	0.982	0.993	adhd.pgs - cing - wor	single
0.002	0.000	0.004	m	0.068	0.272	adhd.pgs - cing - psy	single

0.000	-0.001	0.001	m	0.888	0.989	adhd.pgs - cing - dep	single
0.001	-0.001	0.002	m	0.454	0.743	adhd.pgs - cing - ina	single
0.002	0.000	0.003	m	0.007	0.205	adhd.pgs - cing - tir	single
0.001	0.000	0.003	m	0.040	0.225	adhd.pgs - cing - int	single
0.002	0.000	0.003	m	0.027	0.225	adhd.pgs - cing - app	single
0.000	-0.002	0.002	m	0.788	0.985	adhd.pgs - cing - sui	single
-0.001	-0.002	0.000	m	0.200	0.533	adhd.pgs - cing - 0	single
0.001	0.000	0.002	m	0.015	0.222	adhd.pgs - cing - anx	single
0.000	-0.001	0.002	m	0.456	0.743	adhd.pgs - cing - wor	single
-0.001	-0.002	0.001	m	0.248	0.572	adhd.pgs - cing - psy	single
0.001	0.000	0.003	m	0.118	0.393	adhd.pgs - cing - dep	single
0.000	-0.001	0.002	m	0.497	0.750	adhd.pgs - cing - ina	single
0.000	-0.001	0.001	m	0.752	0.971	adhd.pgs - cing - tir	single
-0.005	-0.029	0.019	b	0.688	0.822	mofc - anx	single
0.001	-0.024	0.025	b	0.943	0.950	fusi - anx	single
0.005	-0.020	0.030	b	0.702	0.822	ins - anx	single
-0.003	-0.027	0.021	b	0.806	0.888	hip - anx	single
0.006	-0.017	0.029	b	0.603	0.772	cing - anx	single
0.028	0.006	0.050	c	0.011	0.051	bd.pgs - anx	single
-0.017	-0.041	0.008	b	0.178	0.368	mofc - wor	single
-0.020	-0.046	0.005	b	0.116	0.267	fusi - wor	single
-0.006	-0.032	0.020	b	0.642	0.791	ins - wor	single
0.005	-0.021	0.030	b	0.720	0.827	hip - wor	single
-0.003	-0.027	0.021	b	0.778	0.873	cing - wor	single
0.045	0.023	0.067	c	0.000	0.004	bd.pgs - wor	single
-0.052	-0.092	-0.013	b	0.009	0.051	mofc - psy	single
-0.045	-0.086	-0.003	b	0.035	0.104	fusi - psy	single
-0.041	-0.083	0.000	b	0.050	0.130	ins - psy	single
-0.027	-0.067	0.013	b	0.188	0.372	hip - psy	single
-0.041	-0.079	-0.003	b	0.035	0.104	cing - psy	single
0.060	0.023	0.097	c	0.002	0.020	bd.pgs - psy	single
-0.014	-0.039	0.011	b	0.272	0.491	mofc - dep	single
-0.013	-0.039	0.013	b	0.334	0.536	fusi - dep	single
-0.009	-0.035	0.017	b	0.508	0.723	ins - dep	single
-0.021	-0.047	0.005	b	0.109	0.256	hip - dep	single
-0.005	-0.029	0.020	b	0.708	0.822	cing - dep	single
0.033	0.010	0.055	c	0.005	0.033	bd.pgs - dep	single
-0.011	-0.038	0.016	b	0.433	0.653	mofc - ina	single
-0.024	-0.051	0.004	b	0.088	0.216	fusi - ina	single
-0.015	-0.043	0.012	b	0.267	0.491	ins - ina	single
-0.036	-0.063	-0.008	b	0.011	0.051	hip - ina	single

-0.012	-0.038	0.013	b	0.343	0.542	cing - ina	single
0.027	0.003	0.051	c	0.026	0.086	bd.pgs - ina	single
-0.041	-0.063	-0.020	b	0.000	0.004	mofc - tir	single
-0.029	-0.051	-0.007	b	0.010	0.051	fusi - tir	single
-0.037	-0.058	-0.015	b	0.001	0.013	ins - tir	single
-0.023	-0.044	-0.001	b	0.040	0.110	hip - tir	single
-0.035	-0.056	-0.014	b	0.001	0.013	cing - tir	single
0.025	0.006	0.044	c	0.011	0.051	bd.pgs - tir	single
-0.033	-0.059	-0.006	b	0.014	0.054	mofc - int	single
-0.039	-0.066	-0.012	b	0.004	0.033	fusi - int	single
-0.027	-0.055	0.000	b	0.047	0.125	ins - int	single
-0.034	-0.061	-0.008	b	0.011	0.051	hip - int	single
-0.032	-0.057	-0.007	b	0.013	0.054	cing - int	single
0.025	0.002	0.048	c	0.036	0.104	bd.pgs - int	single
-0.040	-0.067	-0.013	b	0.003	0.033	mofc - app	single
-0.007	-0.035	0.021	b	0.620	0.782	fusi - app	single
-0.038	-0.066	-0.010	b	0.008	0.051	ins - app	single
-0.035	-0.062	-0.008	b	0.012	0.052	hip - app	single
-0.036	-0.062	-0.011	b	0.006	0.039	cing - app	single
0.029	0.005	0.052	c	0.018	0.064	bd.pgs - app	single
-0.003	-0.046	0.039	b	0.874	0.912	mofc - sui	single
-0.034	-0.079	0.011	b	0.134	0.294	fusi - sui	single
-0.023	-0.067	0.022	b	0.323	0.535	ins - sui	single
-0.071	-0.117	-0.025	b	0.002	0.027	hip - sui	single
-0.008	-0.050	0.033	b	0.697	0.822	cing - sui	single
0.026	-0.014	0.066	c	0.196	0.381	bd.pgs - sui	single
0.007	-0.020	0.033	b	0.628	0.783	mofc - con	single
-0.003	-0.029	0.024	b	0.835	0.888	fusi - con	single
0.010	-0.017	0.037	b	0.466	0.673	ins - con	single
0.003	-0.023	0.029	b	0.827	0.888	hip - con	single
0.013	-0.012	0.038	b	0.303	0.518	cing - con	single
0.047	0.024	0.071	c	0.000	0.004	bd.pgs - con	single
-0.023	-0.044	-0.002	b	0.029	0.094	mofc - sle	single
-0.007	-0.028	0.015	b	0.544	0.753	fusi - sle	single
-0.016	-0.037	0.006	b	0.154	0.324	ins - sle	single
-0.002	-0.023	0.020	b	0.884	0.912	hip - sle	single
-0.029	-0.049	-0.009	b	0.005	0.033	cing - sle	single
0.028	0.009	0.047	c	0.004	0.033	bd.pgs - sle	single
-0.018	-0.042	0.007	b	0.153	0.324	mofc - irr	single
-0.003	-0.028	0.022	b	0.832	0.888	fusi - irr	single
-0.014	-0.039	0.011	b	0.280	0.497	ins - irr	single
0.008	-0.017	0.033	b	0.531	0.745	hip - irr	single

-0.013	-0.036	0.011	b	0.299	0.518	cing - irr	single
0.028	0.006	0.049	c	0.012	0.052	bd.pgs - irr	single
-0.008	-0.035	0.020	b	0.589	0.762	mofc - fore	single
-0.006	-0.034	0.022	b	0.664	0.808	fusi - fore	single
-0.003	-0.031	0.025	b	0.832	0.888	ins - fore	single
-0.001	-0.029	0.026	b	0.919	0.937	hip - fore	single
0.013	-0.013	0.040	b	0.319	0.535	cing - fore	single
0.030	0.006	0.054	c	0.015	0.054	bd.pgs - fore	single
-0.024	-0.055	0.007	b	0.133	0.294	mofc - res	single
-0.027	-0.059	0.004	b	0.091	0.220	fusi - res	single
-0.022	-0.055	0.010	b	0.183	0.370	ins - res	single
-0.035	-0.067	-0.002	b	0.036	0.104	hip - res	single
-0.028	-0.059	0.002	b	0.068	0.171	cing - res	single
0.030	0.002	0.058	c	0.039	0.109	bd.pgs - res	single
-0.011	-0.035	0.013	b	0.352	0.547	mofc - rel	single
-0.012	-0.037	0.012	b	0.332	0.536	fusi - rel	single
-0.007	-0.032	0.018	b	0.560	0.758	ins - rel	single
-0.001	-0.025	0.024	b	0.950	0.950	hip - rel	single
-0.011	-0.034	0.013	b	0.373	0.571	cing - rel	single
0.037	0.015	0.059	c	0.001	0.013	bd.pgs - rel	single
-0.006	-0.029	0.016	b	0.580	0.761	mofc - wor.t	single
-0.013	-0.037	0.010	b	0.264	0.491	fusi - wor.t	single
-0.007	-0.031	0.017	b	0.571	0.759	ins - wor.t	single
0.009	-0.015	0.033	b	0.459	0.671	hip - wor.t	single
-0.007	-0.029	0.016	b	0.563	0.758	cing - wor.t	single
0.037	0.016	0.058	c	0.000	0.011	bd.pgs - wor.t	single
-0.006	-0.021	0.009	a	0.449	0.666	bd.pgs - mofc	single
0.001	-0.014	0.016	a	0.885	0.912	bd.pgs - fusi	single
0.018	0.004	0.033	a	0.014	0.054	bd.pgs - ins	single
-0.002	-0.017	0.012	a	0.756	0.858	bd.pgs - hip	single
0.009	-0.006	0.024	a	0.249	0.475	bd.pgs - cing	single
0.028	0.007	0.050	t	0.011	0.021	bd.pgs - anx	single
0.045	0.022	0.067	t	0.000	0.001	bd.pgs - wor	single
0.059	0.022	0.097	t	0.002	0.006	bd.pgs - psy	single
0.033	0.010	0.055	t	0.005	0.011	bd.pgs - dep	single
0.027	0.003	0.051	t	0.027	0.034	bd.pgs - ina	single
0.024	0.005	0.044	t	0.013	0.021	bd.pgs - tir	single
0.024	0.001	0.047	t	0.040	0.045	bd.pgs - int	single
0.028	0.004	0.052	t	0.021	0.028	bd.pgs - app	single
0.026	-0.014	0.066	t	0.202	0.202	bd.pgs - sui	single
0.048	0.024	0.071	t	0.000	0.001	bd.pgs - con	single
0.027	0.008	0.046	t	0.005	0.011	bd.pgs - sle	single

0.027	0.006	0.049	t	0.013	0.021	bd.pgs - irr	single
0.030	0.006	0.054	t	0.015	0.021	bd.pgs - fore	single
0.029	0.001	0.058	t	0.042	0.045	bd.pgs - res	single
0.037	0.015	0.059	t	0.001	0.003	bd.pgs - rel	single
0.037	0.016	0.058	t	0.000	0.002	bd.pgs - wor.t	single
0.000	0.000	0.001	m tot	0.485	0.825	bd.pgs - anx	single
0.000	-0.001	0.001	m tot	0.840	0.846	bd.pgs - wor	single
-0.001	-0.003	0.002	m tot	0.525	0.825	bd.pgs - psy	single
0.000	-0.001	0.001	m tot	0.846	0.846	bd.pgs - dep	single
0.000	-0.001	0.001	m tot	0.657	0.825	bd.pgs - ina	single
-0.001	-0.003	0.001	m tot	0.461	0.825	bd.pgs - tir	single
-0.001	-0.002	0.001	m tot	0.565	0.825	bd.pgs - int	single
-0.001	-0.003	0.001	m tot	0.459	0.825	bd.pgs - app	single
0.000	-0.002	0.001	m tot	0.718	0.825	bd.pgs - sui	single
0.000	0.000	0.001	m tot	0.447	0.825	bd.pgs - con	single
0.000	-0.001	0.001	m tot	0.424	0.825	bd.pgs - sle	single
0.000	-0.001	0.000	m tot	0.450	0.825	bd.pgs - irr	single
0.000	0.000	0.001	m tot	0.722	0.825	bd.pgs - fore	single
0.000	-0.002	0.001	m tot	0.574	0.825	bd.pgs - res	single
0.000	-0.001	0.001	m tot	0.624	0.825	bd.pgs - rel	single
0.000	-0.001	0.000	m tot	0.547	0.825	bd.pgs - wor.t	single
0.000	0.000	0.000	m	NA	NA	bd.pgs - mofc - anx	single
0.000	0.000	0.000	m	0.509	1.000	bd.pgs - mofc - wor	single
0.000	-0.001	0.001	m	0.467	1.000	bd.pgs - mofc - psy	single
0.000	0.000	0.000	m	0.533	1.000	bd.pgs - mofc - dep	single
0.000	0.000	0.000	m	NA	NA	bd.pgs - mofc - ina	single
0.000	0.000	0.001	m	0.457	1.000	bd.pgs - mofc - tir	single
0.000	0.000	0.001	m	0.469	1.000	bd.pgs - mofc - int	single
0.000	0.000	0.001	m	0.463	1.000	bd.pgs - mofc - app	single
0.000	0.000	0.000	m	0.876	1.000	bd.pgs - mofc - sui	single
0.000	0.000	0.000	m	NA	NA	bd.pgs - mofc - 0	single
0.000	0.000	0.001	m	0.474	1.000	bd.pgs - mofc - anx	single
0.000	0.000	0.000	m	0.503	1.000	bd.pgs - mofc - wor	single
0.000	0.000	0.000	m	NA	NA	bd.pgs - mofc - psy	single
0.000	0.000	0.001	m	0.499	1.000	bd.pgs - mofc - dep	single
0.000	0.000	0.000	m	NA	NA	bd.pgs - mofc - ina	single
0.000	0.000	0.000	m	NA	NA	bd.pgs - mofc - tir	single
0.000	0.000	0.000	m	NA	NA	bd.pgs - fusi - anx	single
0.000	0.000	0.000	m	0.885	1.000	bd.pgs - fusi - wor	single
0.000	-0.001	0.001	m	0.885	1.000	bd.pgs - fusi - psy	single
0.000	0.000	0.000	m	NA	NA	bd.pgs - fusi - dep	single
0.000	0.000	0.000	m	0.885	1.000	bd.pgs - fusi - ina	single

0.000	0.000	0.000	m	0.885	1.000	bd.pgs - fusi - tir	single
0.000	-0.001	0.001	m	0.885	1.000	bd.pgs - fusi - int	single
0.000	0.000	0.000	m	NA	NA	bd.pgs - fusi - app	single
0.000	-0.001	0.000	m	0.885	1.000	bd.pgs - fusi - sui	single
0.000	0.000	0.000	m	NA	NA	bd.pgs - fusi - 0	single
0.000	0.000	0.000	m	NA	NA	bd.pgs - fusi - anx	single
0.000	0.000	0.000	m	NA	NA	bd.pgs - fusi - wor	single
0.000	0.000	0.000	m	NA	NA	bd.pgs - fusi - psy	single
0.000	0.000	0.000	m	0.885	1.000	bd.pgs - fusi - dep	single
0.000	0.000	0.000	m	NA	NA	bd.pgs - fusi - ina	single
0.000	0.000	0.000	m	NA	NA	bd.pgs - fusi - tir	single
0.000	0.000	0.001	m	0.705	1.000	bd.pgs - ins - anx	single
0.000	-0.001	0.000	m	0.648	1.000	bd.pgs - ins - wor	single
-0.001	-0.002	0.000	m	0.127	1.000	bd.pgs - ins - psy	single
0.000	-0.001	0.000	m	0.523	1.000	bd.pgs - ins - dep	single
0.000	-0.001	0.000	m	0.312	1.000	bd.pgs - ins - ina	single
-0.001	-0.001	0.000	m	0.049	1.000	bd.pgs - ins - tir	single
0.000	-0.001	0.000	m	0.123	1.000	bd.pgs - ins - int	single
-0.001	-0.001	0.000	m	0.073	1.000	bd.pgs - ins - app	single
0.000	-0.001	0.000	m	0.359	1.000	bd.pgs - ins - sui	single
0.000	0.000	0.001	m	0.485	1.000	bd.pgs - ins - 0	single
0.000	-0.001	0.000	m	0.218	1.000	bd.pgs - ins - anx	single
0.000	-0.001	0.000	m	0.323	1.000	bd.pgs - ins - wor	single
0.000	-0.001	0.000	m	0.833	1.000	bd.pgs - ins - psy	single
0.000	-0.001	0.000	m	0.242	1.000	bd.pgs - ins - dep	single
0.000	-0.001	0.000	m	0.571	1.000	bd.pgs - ins - ina	single
0.000	-0.001	0.000	m	0.581	1.000	bd.pgs - ins - tir	single
0.000	0.000	0.000	m	NA	NA	bd.pgs - hip - anx	single
0.000	0.000	0.000	m	NA	NA	bd.pgs - hip - wor	single
0.000	0.000	0.000	m	0.762	1.000	bd.pgs - hip - psy	single
0.000	0.000	0.000	m	0.760	1.000	bd.pgs - hip - dep	single
0.000	0.000	0.001	m	0.757	1.000	bd.pgs - hip - ina	single
0.000	0.000	0.000	m	0.758	1.000	bd.pgs - hip - tir	single
0.000	0.000	0.001	m	0.757	1.000	bd.pgs - hip - int	single
0.000	0.000	0.001	m	0.758	1.000	bd.pgs - hip - app	single
0.000	-0.001	0.001	m	0.757	1.000	bd.pgs - hip - sui	single
0.000	0.000	0.000	m	NA	NA	bd.pgs - hip - 0	single
0.000	0.000	0.000	m	NA	NA	bd.pgs - hip - anx	single
0.000	0.000	0.000	m	NA	NA	bd.pgs - hip - wor	single
0.000	0.000	0.000	m	NA	NA	bd.pgs - hip - psy	single
0.000	0.000	0.001	m	0.758	1.000	bd.pgs - hip - dep	single
0.000	0.000	0.000	m	NA	NA	bd.pgs - hip - ina	single

0.000	0.000	0.000	m	NA	NA	bd.pgs - hip - tir	single
0.000	0.000	0.000	m	NA	NA	bd.pgs - cing - anx	single
0.000	0.000	0.000	m	NA	NA	bd.pgs - cing - wor	single
0.000	-0.001	0.000	m	0.312	1.000	bd.pgs - cing - psy	single
0.000	0.000	0.000	m	NA	NA	bd.pgs - cing - dep	single
0.000	0.000	0.000	m	0.464	1.000	bd.pgs - cing - ina	single
0.000	-0.001	0.000	m	0.276	1.000	bd.pgs - cing - tir	single
0.000	-0.001	0.000	m	0.296	1.000	bd.pgs - cing - int	single
0.000	-0.001	0.000	m	0.288	1.000	bd.pgs - cing - app	single
0.000	0.000	0.000	m	0.712	1.000	bd.pgs - cing - sui	single
0.000	0.000	0.000	m	0.442	1.000	bd.pgs - cing - 0	single
0.000	-0.001	0.000	m	0.286	1.000	bd.pgs - cing - anx	single
0.000	0.000	0.000	m	0.440	1.000	bd.pgs - cing - wor	single
0.000	0.000	0.000	m	0.451	1.000	bd.pgs - cing - psy	single
0.000	-0.001	0.000	m	0.330	1.000	bd.pgs - cing - dep	single
0.000	0.000	0.000	m	0.481	1.000	bd.pgs - cing - ina	single
0.000	0.000	0.000	m	NA	NA	bd.pgs - cing - tir	single
-0.004	-0.028	0.019	b	0.713	0.814	mofc - anx	single
0.001	-0.023	0.026	b	0.926	0.944	fusi - anx	single
0.006	-0.019	0.031	b	0.649	0.780	ins - anx	single
-0.003	-0.027	0.022	b	0.838	0.905	hip - anx	single
0.007	-0.016	0.030	b	0.565	0.751	cing - anx	single
0.023	0.001	0.045	c	0.041	0.130	scz.pgs - anx	single
-0.016	-0.041	0.008	b	0.196	0.391	mofc - wor	single
-0.020	-0.045	0.006	b	0.126	0.288	fusi - wor	single
-0.005	-0.031	0.021	b	0.717	0.814	ins - wor	single
0.005	-0.020	0.030	b	0.687	0.806	hip - wor	single
-0.003	-0.026	0.021	b	0.838	0.905	cing - wor	single
0.034	0.011	0.057	c	0.003	0.030	scz.pgs - wor	single
-0.052	-0.091	-0.012	b	0.010	0.056	mofc - psy	single
-0.044	-0.085	-0.002	b	0.038	0.125	fusi - psy	single
-0.039	-0.081	0.002	b	0.062	0.162	ins - psy	single
-0.026	-0.066	0.014	b	0.205	0.391	hip - psy	single
-0.039	-0.078	-0.001	b	0.043	0.132	cing - psy	single
0.055	0.017	0.093	c	0.004	0.031	scz.pgs - psy	single
-0.014	-0.039	0.012	b	0.290	0.508	mofc - dep	single
-0.013	-0.039	0.014	b	0.348	0.541	fusi - dep	single
-0.008	-0.034	0.019	b	0.563	0.751	ins - dep	single
-0.021	-0.047	0.005	b	0.117	0.276	hip - dep	single
-0.004	-0.028	0.020	b	0.749	0.841	cing - dep	single
0.025	0.002	0.048	c	0.034	0.117	scz.pgs - dep	single
-0.010	-0.037	0.017	b	0.472	0.671	mofc - ina	single

-0.024	-0.051	0.004	b	0.091	0.224	fusi - ina	single
-0.014	-0.042	0.013	b	0.300	0.513	ins - ina	single
-0.035	-0.062	-0.008	b	0.012	0.058	hip - ina	single
-0.012	-0.037	0.014	b	0.376	0.576	cing - ina	single
0.040	0.016	0.064	c	0.001	0.019	scz.pgs - ina	single
-0.041	-0.062	-0.019	b	0.000	0.006	mofc - tir	single
-0.029	-0.051	-0.007	b	0.010	0.056	fusi - tir	single
-0.036	-0.057	-0.014	b	0.001	0.019	ins - tir	single
-0.022	-0.043	0.000	b	0.047	0.136	hip - tir	single
-0.034	-0.055	-0.013	b	0.001	0.019	cing - tir	single
0.031	0.011	0.050	c	0.002	0.023	scz.pgs - tir	single
-0.032	-0.058	-0.006	b	0.016	0.066	mofc - int	single
-0.039	-0.066	-0.012	b	0.005	0.031	fusi - int	single
-0.026	-0.054	0.001	b	0.056	0.152	ins - int	single
-0.034	-0.060	-0.007	b	0.013	0.058	hip - int	single
-0.031	-0.057	-0.006	b	0.016	0.066	cing - int	single
0.024	0.000	0.047	c	0.049	0.139	scz.pgs - int	single
-0.039	-0.066	-0.012	b	0.004	0.031	mofc - app	single
-0.006	-0.034	0.021	b	0.646	0.780	fusi - app	single
-0.036	-0.064	-0.008	b	0.011	0.056	ins - app	single
-0.034	-0.061	-0.007	b	0.015	0.064	hip - app	single
-0.035	-0.061	-0.009	b	0.008	0.048	cing - app	single
0.052	0.028	0.076	c	0.000	0.002	scz.pgs - app	single
-0.003	-0.046	0.040	b	0.889	0.933	mofc - sui	single
-0.034	-0.079	0.011	b	0.140	0.307	fusi - sui	single
-0.022	-0.066	0.023	b	0.339	0.541	ins - sui	single
-0.071	-0.117	-0.025	b	0.003	0.028	hip - sui	single
-0.008	-0.049	0.034	b	0.713	0.814	cing - sui	single
0.014	-0.026	0.053	c	0.493	0.691	scz.pgs - sui	single
0.008	-0.019	0.034	b	0.577	0.757	mofc - con	single
-0.003	-0.029	0.024	b	0.851	0.905	fusi - con	single
0.011	-0.015	0.038	b	0.401	0.596	ins - con	single
0.004	-0.022	0.030	b	0.769	0.854	hip - con	single
0.014	-0.011	0.039	b	0.261	0.479	cing - con	single
0.047	0.023	0.071	c	0.000	0.005	scz.pgs - con	single
-0.023	-0.044	-0.002	b	0.031	0.113	mofc - sle	single
-0.006	-0.028	0.015	b	0.555	0.751	fusi - sle	single
-0.015	-0.036	0.007	b	0.176	0.364	ins - sle	single
-0.001	-0.023	0.020	b	0.914	0.942	hip - sle	single
-0.029	-0.049	-0.008	b	0.005	0.034	cing - sle	single
0.018	-0.001	0.037	c	0.060	0.160	scz.pgs - sle	single
-0.018	-0.042	0.007	b	0.159	0.334	mofc - irr	single

-0.003	-0.028	0.023	b	0.843	0.905	fusi - irr	single
-0.013	-0.038	0.012	b	0.310	0.522	ins - irr	single
0.008	-0.017	0.033	b	0.516	0.713	hip - irr	single
-0.012	-0.036	0.012	b	0.321	0.531	cing - irr	single
0.016	-0.006	0.038	c	0.154	0.330	scz.pgs - irr	single
-0.007	-0.034	0.020	b	0.626	0.780	mofc - fore	single
-0.006	-0.034	0.021	b	0.657	0.780	fusi - fore	single
-0.002	-0.030	0.026	b	0.896	0.933	ins - fore	single
-0.001	-0.028	0.027	b	0.955	0.965	hip - fore	single
0.014	-0.012	0.040	b	0.292	0.508	cing - fore	single
0.029	0.004	0.053	c	0.024	0.088	scz.pgs - fore	single
-0.024	-0.055	0.008	b	0.138	0.307	mofc - res	single
-0.027	-0.059	0.005	b	0.095	0.229	fusi - res	single
-0.021	-0.054	0.011	b	0.203	0.391	ins - res	single
-0.034	-0.067	-0.002	b	0.038	0.125	hip - res	single
-0.028	-0.058	0.003	b	0.074	0.186	cing - res	single
0.017	-0.011	0.046	c	0.242	0.452	scz.pgs - res	single
-0.011	-0.034	0.013	b	0.382	0.576	mofc - rel	single
-0.012	-0.036	0.013	b	0.344	0.541	fusi - rel	single
-0.006	-0.031	0.019	b	0.625	0.780	ins - rel	single
0.000	-0.025	0.024	b	0.986	0.986	hip - rel	single
-0.010	-0.033	0.014	b	0.415	0.608	cing - rel	single
0.033	0.011	0.056	c	0.003	0.030	scz.pgs - rel	single
-0.006	-0.029	0.017	b	0.605	0.777	mofc - wor.t	single
-0.013	-0.037	0.010	b	0.274	0.494	fusi - wor.t	single
-0.006	-0.030	0.018	b	0.636	0.780	ins - wor.t	single
0.009	-0.014	0.033	b	0.437	0.630	hip - wor.t	single
-0.006	-0.028	0.016	b	0.608	0.777	cing - wor.t	single
0.025	0.004	0.046	c	0.021	0.082	scz.pgs - wor.t	single
-0.024	-0.039	-0.009	a	0.001	0.019	scz.pgs - mofc	single
-0.007	-0.022	0.008	a	0.341	0.541	scz.pgs - fusi	single
-0.009	-0.024	0.005	a	0.199	0.391	scz.pgs - ins	single
-0.021	-0.036	-0.007	a	0.004	0.031	scz.pgs - hip	single
-0.015	-0.031	0.000	a	0.047	0.136	scz.pgs - cing	single
0.023	0.001	0.045	t	0.041	0.055	scz.pgs - anx	single
0.035	0.012	0.057	t	0.003	0.006	scz.pgs - wor	single
0.059	0.021	0.096	t	0.002	0.006	scz.pgs - psy	single
0.026	0.003	0.049	t	0.027	0.043	scz.pgs - dep	single
0.041	0.017	0.065	t	0.001	0.003	scz.pgs - ina	single
0.033	0.014	0.053	t	0.001	0.003	scz.pgs - tir	single
0.026	0.003	0.050	t	0.029	0.043	scz.pgs - int	single
0.055	0.031	0.079	t	0.000	0.000	scz.pgs - app	single

0.016	-0.023	0.055	t	0.427	0.427	scz.pgs - sui	single
0.047	0.023	0.071	t	0.000	0.001	scz.pgs - con	single
0.019	0.000	0.038	t	0.045	0.055	scz.pgs - sle	single
0.017	-0.005	0.039	t	0.139	0.159	scz.pgs - irr	single
0.029	0.004	0.053	t	0.023	0.041	scz.pgs - fore	single
0.019	-0.009	0.048	t	0.187	0.199	scz.pgs - res	single
0.034	0.012	0.056	t	0.002	0.006	scz.pgs - rel	single
0.025	0.004	0.046	t	0.020	0.040	scz.pgs - wor.t	single
0.000	-0.001	0.001	m tot	0.995	0.995	scz.pgs - anx	single
0.001	-0.001	0.002	m tot	0.518	0.638	scz.pgs - wor	single
0.003	0.000	0.006	m tot	0.063	0.250	scz.pgs - psy	single
0.001	-0.001	0.003	m tot	0.228	0.406	scz.pgs - dep	single
0.001	0.000	0.003	m tot	0.125	0.287	scz.pgs - ina	single
0.003	0.000	0.005	m tot	0.025	0.200	scz.pgs - tir	single
0.003	0.000	0.005	m tot	0.038	0.200	scz.pgs - int	single
0.003	0.000	0.005	m tot	0.028	0.200	scz.pgs - app	single
0.002	-0.001	0.005	m tot	0.161	0.321	scz.pgs - sui	single
-0.001	-0.002	0.001	m tot	0.478	0.637	scz.pgs - con	single
0.001	0.000	0.003	m tot	0.122	0.287	scz.pgs - sle	single
0.001	-0.001	0.002	m tot	0.459	0.637	scz.pgs - irr	single
0.000	-0.002	0.002	m tot	0.975	0.995	scz.pgs - fore	single
0.002	0.000	0.004	m tot	0.078	0.250	scz.pgs - res	single
0.001	-0.001	0.002	m tot	0.466	0.637	scz.pgs - rel	single
0.000	-0.001	0.002	m tot	0.796	0.910	scz.pgs - wor.t	single
0.000	0.000	0.001	m	0.715	0.895	scz.pgs - mofc - anx	single
0.000	0.000	0.001	m	0.230	0.788	scz.pgs - mofc - wor	single
0.001	0.000	0.002	m	0.045	0.634	scz.pgs - mofc - psy	single
0.000	0.000	0.001	m	0.315	0.788	scz.pgs - mofc - dep	single
0.000	0.000	0.001	m	0.482	0.788	scz.pgs - mofc - ina	single
0.001	0.000	0.002	m	0.015	0.634	scz.pgs - mofc - tir	single
0.001	0.000	0.002	m	0.054	0.634	scz.pgs - mofc - int	single
0.001	0.000	0.002	m	0.033	0.634	scz.pgs - mofc - app	single
0.000	-0.001	0.001	m	0.889	1.000	scz.pgs - mofc - sui	single
0.000	-0.001	0.000	m	0.583	0.863	scz.pgs - mofc - 0	single
0.001	0.000	0.001	m	0.074	0.640	scz.pgs - mofc - anx	single
0.000	0.000	0.001	m	0.197	0.787	scz.pgs - mofc - wor	single
0.000	-0.001	0.001	m	0.630	0.869	scz.pgs - mofc - psy	single
0.001	0.000	0.001	m	0.178	0.773	scz.pgs - mofc - dep	single
0.000	0.000	0.001	m	0.399	0.788	scz.pgs - mofc - ina	single
0.000	0.000	0.001	m	0.610	0.869	scz.pgs - mofc - tir	single
0.000	0.000	0.000	m	NA	NA	scz.pgs - fusi - anx	single
0.000	0.000	0.000	m	0.419	0.788	scz.pgs - fusi - wor	single

0.000	0.000	0.001	m	0.387	0.788	scz.pgs - fusi - psy	single
0.000	0.000	0.000	m	0.504	0.791	scz.pgs - fusi - dep	single
0.000	0.000	0.001	m	0.407	0.788	scz.pgs - fusi - ina	single
0.000	0.000	0.001	m	0.372	0.788	scz.pgs - fusi - tir	single
0.000	0.000	0.001	m	0.367	0.788	scz.pgs - fusi - int	single
0.000	0.000	0.000	m	NA	NA	scz.pgs - fusi - app	single
0.000	0.000	0.001	m	0.424	0.788	scz.pgs - fusi - sui	single
0.000	0.000	0.000	m	NA	NA	scz.pgs - fusi - 0	single
0.000	0.000	0.000	m	NA	NA	scz.pgs - fusi - anx	single
0.000	0.000	0.000	m	NA	NA	scz.pgs - fusi - wor	single
0.000	0.000	0.000	m	NA	NA	scz.pgs - fusi - psy	single
0.000	0.000	0.001	m	0.408	0.788	scz.pgs - fusi - dep	single
0.000	0.000	0.000	m	0.502	0.791	scz.pgs - fusi - ina	single
0.000	0.000	0.000	m	0.473	0.788	scz.pgs - fusi - tir	single
0.000	0.000	0.000	m	0.668	0.876	scz.pgs - ins - anx	single
0.000	0.000	0.000	m	0.727	0.895	scz.pgs - ins - wor	single
0.000	0.000	0.001	m	0.290	0.788	scz.pgs - ins - psy	single
0.000	0.000	0.000	m	0.598	0.869	scz.pgs - ins - dep	single
0.000	0.000	0.000	m	0.420	0.788	scz.pgs - ins - ina	single
0.000	0.000	0.001	m	0.233	0.788	scz.pgs - ins - tir	single
0.000	0.000	0.001	m	0.286	0.788	scz.pgs - ins - int	single
0.000	0.000	0.001	m	0.252	0.788	scz.pgs - ins - app	single
0.000	0.000	0.001	m	0.443	0.788	scz.pgs - ins - sui	single
0.000	0.000	0.000	m	0.482	0.788	scz.pgs - ins - 0	single
0.000	0.000	0.000	m	0.352	0.788	scz.pgs - ins - anx	single
0.000	0.000	0.000	m	0.426	0.788	scz.pgs - ins - wor	single
0.000	0.000	0.000	m	0.896	1.000	scz.pgs - ins - psy	single
0.000	0.000	0.001	m	0.366	0.788	scz.pgs - ins - dep	single
0.000	0.000	0.000	m	0.648	0.876	scz.pgs - ins - ina	single
0.000	0.000	0.000	m	0.657	0.876	scz.pgs - ins - tir	single
0.000	0.000	0.001	m	0.838	0.972	scz.pgs - hip - anx	single
0.000	-0.001	0.000	m	0.689	0.890	scz.pgs - hip - wor	single
0.001	0.000	0.002	m	0.247	0.788	scz.pgs - hip - psy	single
0.000	0.000	0.001	m	0.170	0.773	scz.pgs - hip - dep	single
0.001	0.000	0.002	m	0.060	0.634	scz.pgs - hip - ina	single
0.000	0.000	0.001	m	0.103	0.640	scz.pgs - hip - tir	single
0.001	0.000	0.001	m	0.060	0.634	scz.pgs - hip - int	single
0.001	0.000	0.001	m	0.063	0.634	scz.pgs - hip - app	single
0.002	0.000	0.003	m	0.038	0.634	scz.pgs - hip - sui	single
0.000	-0.001	0.000	m	0.771	0.920	scz.pgs - hip - 0	single
0.000	0.000	0.000	m	0.914	1.000	scz.pgs - hip - anx	single
0.000	-0.001	0.000	m	0.526	0.809	scz.pgs - hip - wor	single

0.000	-0.001	0.001	m	0.955	1.000	scz.pgs - hip - psy	single
0.001	0.000	0.002	m	0.094	0.640	scz.pgs - hip - dep	single
0.000	-0.001	0.001	m	0.986	1.000	scz.pgs - hip - ina	single
0.000	-0.001	0.000	m	0.453	0.788	scz.pgs - hip - tir	single
0.000	0.000	0.000	m	0.581	0.863	scz.pgs - cing - anx	single
0.000	0.000	0.000	m	0.838	0.972	scz.pgs - cing - wor	single
0.001	0.000	0.001	m	0.156	0.773	scz.pgs - cing - psy	single
0.000	0.000	0.000	m	0.752	0.912	scz.pgs - cing - dep	single
0.000	0.000	0.001	m	0.419	0.788	scz.pgs - cing - ina	single
0.001	0.000	0.001	m	0.091	0.640	scz.pgs - cing - tir	single
0.000	0.000	0.001	m	0.125	0.666	scz.pgs - cing - int	single
0.001	0.000	0.001	m	0.112	0.640	scz.pgs - cing - app	single
0.000	-0.001	0.001	m	0.718	0.895	scz.pgs - cing - sui	single
0.000	-0.001	0.000	m	0.328	0.788	scz.pgs - cing - 0	single
0.000	0.000	0.001	m	0.106	0.640	scz.pgs - cing - anx	single
0.000	0.000	0.001	m	0.375	0.788	scz.pgs - cing - wor	single
0.000	-0.001	0.000	m	0.352	0.788	scz.pgs - cing - psy	single
0.000	0.000	0.001	m	0.184	0.773	scz.pgs - cing - dep	single
0.000	0.000	0.001	m	0.451	0.788	scz.pgs - cing - ina	single
0.000	0.000	0.000	m	0.619	0.869	scz.pgs - cing - tir	single
-0.002	-0.026	0.022	b	0.846	0.919	mofc - anx	multiple
0.003	-0.022	0.027	b	0.814	0.914	fusi - anx	multiple
0.008	-0.017	0.032	b	0.546	0.722	ins - anx	multiple
-0.002	-0.026	0.023	b	0.887	0.944	hip - anx	multiple
0.008	-0.015	0.032	b	0.475	0.649	cing - anx	multiple
0.049	0.026	0.071	c	0.000	0.000	dep.pgs - anx	multiple
0.014	-0.009	0.036	c	0.234	0.427	adhd.pgs - anx	multiple
0.008	-0.017	0.032	c	0.540	0.720	scz.pgs - anx	multiple
0.013	-0.011	0.037	c	0.281	0.465	bd.pgs - anx	multiple
-0.014	-0.038	0.011	b	0.272	0.460	mofc - wor	multiple
-0.018	-0.043	0.007	b	0.168	0.338	fusi - wor	multiple
-0.002	-0.028	0.023	b	0.850	0.919	ins - wor	multiple
0.006	-0.019	0.032	b	0.616	0.789	hip - wor	multiple
0.000	-0.024	0.024	b	0.975	0.995	cing - wor	multiple
0.043	0.019	0.066	c	0.000	0.003	dep.pgs - wor	multiple
0.024	0.001	0.047	c	0.045	0.139	adhd.pgs - wor	multiple
0.013	-0.012	0.037	c	0.320	0.510	scz.pgs - wor	multiple
0.028	0.004	0.053	c	0.024	0.087	bd.pgs - wor	multiple
-0.048	-0.087	-0.008	b	0.018	0.074	mofc - psy	multiple

-0.041	-0.082	0.000	b	0.052	0.150	fusi - psy	multiple
-0.036	-0.078	0.005	b	0.087	0.224	ins - psy	multiple
-0.024	-0.064	0.016	b	0.247	0.437	hip - psy	multiple
-0.036	-0.075	0.002	b	0.061	0.164	cing - psy	multiple
0.046	0.007	0.084	c	0.021	0.080	dep.pgs - psy	multiple
0.035	-0.004	0.073	c	0.076	0.197	adhd.pgs - psy	multiple
0.029	-0.012	0.071	c	0.165	0.338	scz.pgs - psy	multiple
0.035	-0.006	0.076	c	0.095	0.232	bd.pgs - psy	multiple
-0.010	-0.036	0.015	b	0.415	0.619	mofc - dep	multiple
-0.010	-0.036	0.017	b	0.473	0.649	fusi - dep	multiple
-0.005	-0.031	0.022	b	0.735	0.876	ins - dep	multiple
-0.019	-0.045	0.007	b	0.144	0.306	hip - dep	multiple
-0.001	-0.026	0.023	b	0.926	0.973	cing - dep	multiple
0.063	0.039	0.087	c	0.000	0.000	dep.pgs - dep	multiple
0.023	-0.001	0.047	c	0.057	0.156	adhd.pgs - dep	multiple
0.005	-0.020	0.030	c	0.684	0.850	scz.pgs - dep	multiple
0.014	-0.011	0.039	c	0.263	0.449	bd.pgs - dep	multiple
-0.007	-0.034	0.020	b	0.595	0.774	mofc - ina	multiple
-0.021	-0.049	0.006	b	0.126	0.282	fusi - ina	multiple
-0.012	-0.039	0.015	b	0.395	0.599	ins - ina	multiple
-0.034	-0.061	-0.006	b	0.015	0.068	hip - ina	multiple
-0.010	-0.035	0.016	b	0.467	0.649	cing - ina	multiple
0.039	0.014	0.065	c	0.002	0.015	dep.pgs - ina	multiple
0.018	-0.007	0.044	c	0.160	0.335	adhd.pgs - ina	multiple
0.029	0.002	0.055	c	0.032	0.108	scz.pgs - ina	multiple
0.005	-0.021	0.031	c	0.703	0.854	bd.pgs - ina	multiple
-0.037	-0.058	-0.016	b	0.001	0.005	mofc - tir	multiple
-0.025	-0.047	-0.003	b	0.023	0.087	fusi - tir	multiple
-0.032	-0.053	-0.010	b	0.004	0.025	ins - tir	multiple
-0.020	-0.042	0.001	b	0.067	0.176	hip - tir	multiple
-0.030	-0.051	-0.010	b	0.004	0.024	cing - tir	multiple
0.063	0.043	0.084	c	0.000	0.000	dep.pgs - tir	multiple
0.034	0.013	0.054	c	0.001	0.008	adhd.pgs - tir	multiple
0.015	-0.006	0.036	c	0.170	0.338	scz.pgs - tir	multiple
0.002	-0.019	0.023	c	0.850	0.919	bd.pgs - tir	multiple
-0.028	-0.054	-0.002	b	0.035	0.114	mofc - int	multiple

-0.036	-0.062	-0.009	b	0.009	0.047	fusi - int	multiple
-0.022	-0.049	0.005	b	0.106	0.249	ins - int	multiple
-0.032	-0.058	-0.005	b	0.019	0.074	hip - int	multiple
-0.028	-0.053	-0.002	b	0.032	0.108	cing - int	multiple
0.060	0.035	0.085	c	0.000	0.000	dep.pgs - int	multiple
0.033	0.008	0.058	c	0.011	0.051	adhd.pgs - int	multiple
0.007	-0.019	0.032	c	0.607	0.784	scz.pgs - int	multiple
0.006	-0.020	0.031	c	0.670	0.845	bd.pgs - int	multiple
-0.033	-0.060	-0.006	b	0.016	0.068	mofc - app	multiple
-0.002	-0.029	0.026	b	0.908	0.960	fusi - app	multiple
-0.030	-0.058	-0.002	b	0.036	0.117	ins - app	multiple
-0.031	-0.058	-0.004	b	0.027	0.094	hip - app	multiple
-0.030	-0.055	-0.004	b	0.024	0.087	cing - app	multiple
0.053	0.028	0.078	c	0.000	0.000	dep.pgs - app	multiple
0.061	0.036	0.086	c	0.000	0.000	adhd.pgs - app	multiple
0.038	0.011	0.064	c	0.005	0.030	scz.pgs - app	multiple
-0.005	-0.031	0.022	c	0.725	0.874	bd.pgs - app	multiple
0.000	-0.042	0.042	b	1.000	1.000	mofc - sui	multiple
-0.032	-0.076	0.013	b	0.163	0.338	fusi - sui	multiple
-0.019	-0.063	0.026	b	0.406	0.611	ins - sui	multiple
-0.070	-0.116	-0.024	b	0.003	0.018	hip - sui	multiple
-0.005	-0.046	0.036	b	0.812	0.914	cing - sui	multiple
0.052	0.011	0.094	c	0.014	0.065	dep.pgs - sui	multiple
0.029	-0.012	0.070	c	0.171	0.338	adhd.pgs - sui	multiple
-0.004	-0.048	0.040	c	0.852	0.919	scz.pgs - sui	multiple
0.014	-0.031	0.058	c	0.551	0.722	bd.pgs - sui	multiple
0.011	-0.016	0.037	b	0.432	0.622	mofc - con	multiple
0.000	-0.026	0.027	b	0.993	1.000	fusi - con	multiple
0.014	-0.012	0.041	b	0.286	0.469	ins - con	multiple
0.005	-0.021	0.032	b	0.689	0.850	hip - con	multiple
0.017	-0.008	0.042	b	0.185	0.356	cing - con	multiple
0.053	0.028	0.078	c	0.000	0.000	dep.pgs - con	multiple
0.030	0.005	0.055	c	0.018	0.074	adhd.pgs - con	multiple
0.026	-0.001	0.052	c	0.055	0.153	scz.pgs - con	multiple
0.022	-0.004	0.048	c	0.094	0.232	bd.pgs - con	multiple
-0.021	-0.042	0.000	b	0.052	0.150	mofc - sle	multiple

-0.004	-0.026	0.017	b	0.695	0.851	fusi - sle	multiple
-0.013	-0.034	0.009	b	0.248	0.437	ins - sle	multiple
0.000	-0.021	0.021	b	0.998	1.000	hip - sle	multiple
-0.027	-0.047	-0.007	b	0.009	0.047	cing - sle	multiple
0.035	0.015	0.055	c	0.001	0.005	dep.pgs - sle	multiple
0.023	0.003	0.043	c	0.023	0.087	adhd.pgs - sle	multiple
0.003	-0.018	0.023	c	0.808	0.914	scz.pgs - sle	multiple
0.017	-0.004	0.038	c	0.119	0.270	bd.pgs - sle	multiple
-0.014	-0.039	0.010	b	0.256	0.442	mofc - irr	multiple
0.000	-0.025	0.026	b	0.970	0.995	fusi - irr	multiple
-0.010	-0.035	0.016	b	0.448	0.633	ins - irr	multiple
0.010	-0.015	0.035	b	0.437	0.624	hip - irr	multiple
-0.009	-0.033	0.015	b	0.459	0.643	cing - irr	multiple
0.051	0.028	0.075	c	0.000	0.000	dep.pgs - irr	multiple
0.032	0.009	0.055	c	0.006	0.032	adhd.pgs - irr	multiple
-0.002	-0.027	0.022	c	0.851	0.919	scz.pgs - irr	multiple
0.014	-0.010	0.038	c	0.247	0.437	bd.pgs - irr	multiple
-0.004	-0.032	0.023	b	0.748	0.876	mofc - fore	multiple
-0.003	-0.030	0.025	b	0.843	0.919	fusi - fore	multiple
0.001	-0.027	0.028	b	0.971	0.995	ins - fore	multiple
0.000	-0.027	0.028	b	0.976	0.995	hip - fore	multiple
0.016	-0.010	0.042	b	0.226	0.417	cing - fore	multiple
0.057	0.032	0.083	c	0.000	0.000	dep.pgs - fore	multiple
0.020	-0.006	0.045	c	0.127	0.282	adhd.pgs - fore	multiple
0.012	-0.015	0.039	c	0.386	0.591	scz.pgs - fore	multiple
0.011	-0.016	0.037	c	0.422	0.622	bd.pgs - fore	multiple
-0.019	-0.050	0.012	b	0.223	0.416	mofc - res	multiple
-0.024	-0.056	0.008	b	0.136	0.297	fusi - res	multiple
-0.017	-0.050	0.015	b	0.303	0.487	ins - res	multiple
-0.032	-0.064	0.000	b	0.052	0.150	hip - res	multiple
-0.025	-0.055	0.006	b	0.112	0.259	cing - res	multiple
0.047	0.017	0.076	c	0.002	0.014	dep.pgs - res	multiple
0.046	0.017	0.075	c	0.002	0.014	adhd.pgs - res	multiple
-0.003	-0.034	0.028	c	0.868	0.930	scz.pgs - res	multiple
0.015	-0.016	0.047	c	0.331	0.522	bd.pgs - res	multiple
-0.008	-0.032	0.016	b	0.496	0.673	mofc - rel	multiple

-0.010	-0.034	0.015	b	0.432	0.622	fusi - rel	multiple
-0.004	-0.029	0.021	b	0.741	0.876	ins - rel	multiple
0.001	-0.023	0.025	b	0.940	0.982	hip - rel	multiple
-0.008	-0.031	0.015	b	0.512	0.688	cing - rel	multiple
0.053	0.030	0.076	c	0.000	0.000	dep.pgs - rel	multiple
0.016	-0.007	0.038	c	0.181	0.353	adhd.pgs - rel	multiple
0.015	-0.009	0.039	c	0.218	0.412	scz.pgs - rel	multiple
0.018	-0.006	0.042	c	0.138	0.298	bd.pgs - rel	multiple
-0.004	-0.027	0.019	b	0.761	0.885	mofc - wor.t	multiple
-0.011	-0.034	0.013	b	0.367	0.573	fusi - wor.t	multiple
-0.004	-0.027	0.020	b	0.773	0.887	ins - wor.t	multiple
0.011	-0.013	0.034	b	0.380	0.588	hip - wor.t	multiple
-0.004	-0.026	0.019	b	0.743	0.876	cing - wor.t	multiple
0.046	0.024	0.068	c	0.000	0.000	dep.pgs - wor.t	multiple
0.022	0.001	0.044	c	0.045	0.139	adhd.pgs - wor.t	multiple
0.005	-0.018	0.028	c	0.679	0.850	scz.pgs - wor.t	multiple
0.023	0.000	0.046	c	0.049	0.150	bd.pgs - wor.t	multiple
-0.006	-0.022	0.009	a	0.426	0.622	dep.pgs - mofc	multiple
-0.050	-0.065	-0.034	a	0.000	0.000	adhd.pgs - mofc	multiple
-0.020	-0.037	-0.004	a	0.014	0.065	scz.pgs - mofc	multiple
0.009	-0.008	0.026	a	0.293	0.476	bd.pgs - mofc	multiple
-0.013	-0.029	0.002	a	0.091	0.230	dep.pgs - fusi	multiple
-0.038	-0.053	-0.023	a	0.000	0.000	adhd.pgs - fusi	multiple
-0.004	-0.020	0.012	a	0.658	0.836	scz.pgs - fusi	multiple
0.009	-0.007	0.025	a	0.251	0.437	bd.pgs - fusi	multiple
-0.013	-0.028	0.003	a	0.106	0.249	dep.pgs - ins	multiple
-0.049	-0.064	-0.034	a	0.000	0.000	adhd.pgs - ins	multiple
-0.013	-0.029	0.003	a	0.103	0.248	scz.pgs - ins	multiple
0.031	0.015	0.047	a	0.000	0.001	bd.pgs - ins	multiple
0.002	-0.013	0.018	a	0.773	0.887	dep.pgs - hip	multiple
-0.031	-0.046	-0.016	a	0.000	0.000	adhd.pgs - hip	multiple
-0.021	-0.037	-0.005	a	0.009	0.047	scz.pgs - hip	multiple
0.009	-0.007	0.025	a	0.275	0.460	bd.pgs - hip	multiple
-0.010	-0.026	0.006	a	0.217	0.412	dep.pgs - cing	multiple
-0.049	-0.064	-0.033	a	0.000	0.000	adhd.pgs - cing	multiple
-0.016	-0.033	0.000	a	0.053	0.150	scz.pgs - cing	multiple

0.023	0.006	0.040	a	0.008	0.043	bd.pgs - cing	multiple
0.048	0.026	0.071	t	0.000	0.000	dep.pgs - anx	multiple
0.043	0.020	0.067	t	0.000	0.002	dep.pgs - wor	multiple
0.047	0.009	0.086	t	0.016	0.046	dep.pgs - psy	multiple
0.063	0.039	0.087	t	0.000	0.000	dep.pgs - dep	multiple
0.040	0.015	0.065	t	0.002	0.007	dep.pgs - ina	multiple
0.064	0.044	0.085	t	0.000	0.000	dep.pgs - tir	multiple
0.061	0.037	0.086	t	0.000	0.000	dep.pgs - int	multiple
0.054	0.029	0.079	t	0.000	0.000	dep.pgs - app	multiple
0.053	0.011	0.094	t	0.013	0.037	dep.pgs - sui	multiple
0.053	0.028	0.077	t	0.000	0.000	dep.pgs - con	multiple
0.036	0.016	0.056	t	0.000	0.002	dep.pgs - sle	multiple
0.051	0.028	0.075	t	0.000	0.000	dep.pgs - irr	multiple
0.057	0.032	0.083	t	0.000	0.000	dep.pgs - fore	multiple
0.048	0.018	0.077	t	0.001	0.006	dep.pgs - res	multiple
0.053	0.031	0.076	t	0.000	0.000	dep.pgs - rel	multiple
0.047	0.024	0.069	t	0.000	0.000	dep.pgs - wor.t	multiple
0.013	-0.009	0.035	t	0.253	0.368	adhd.pgs - anx	multiple
0.025	0.002	0.048	t	0.032	0.073	adhd.pgs - wor	multiple
0.043	0.005	0.080	t	0.026	0.062	adhd.pgs - psy	multiple
0.025	0.001	0.049	t	0.038	0.081	adhd.pgs - dep	multiple
0.022	-0.004	0.047	t	0.093	0.175	adhd.pgs - ina	multiple
0.040	0.020	0.060	t	0.000	0.000	adhd.pgs - tir	multiple
0.039	0.014	0.063	t	0.002	0.007	adhd.pgs - int	multiple
0.066	0.042	0.091	t	0.000	0.000	adhd.pgs - app	multiple
0.033	-0.007	0.074	t	0.108	0.197	adhd.pgs - sui	multiple
0.028	0.003	0.052	t	0.026	0.062	adhd.pgs - con	multiple
0.026	0.007	0.046	t	0.009	0.027	adhd.pgs - sle	multiple
0.034	0.011	0.056	t	0.003	0.011	adhd.pgs - irr	multiple
0.019	-0.006	0.044	t	0.131	0.215	adhd.pgs - fore	multiple
0.051	0.022	0.079	t	0.001	0.002	adhd.pgs - res	multiple
0.017	-0.006	0.039	t	0.140	0.224	adhd.pgs - rel	multiple
0.023	0.001	0.044	t	0.036	0.080	adhd.pgs - wor.t	multiple
0.007	-0.017	0.031	t	0.548	0.662	scz.pgs - anx	multiple
0.013	-0.012	0.037	t	0.310	0.413	scz.pgs - wor	multiple
0.032	-0.009	0.073	t	0.129	0.215	scz.pgs - psy	multiple

0.006	-0.019	0.031	t	0.642	0.734	scz.pgs - dep	multiple
0.030	0.004	0.056	t	0.025	0.062	scz.pgs - ina	multiple
0.017	-0.004	0.038	t	0.114	0.204	scz.pgs - tir	multiple
0.009	-0.017	0.034	t	0.498	0.613	scz.pgs - int	multiple
0.040	0.014	0.066	t	0.003	0.010	scz.pgs - app	multiple
-0.002	-0.046	0.041	t	0.920	0.950	scz.pgs - sui	multiple
0.025	-0.001	0.051	t	0.063	0.125	scz.pgs - con	multiple
0.004	-0.017	0.024	t	0.732	0.808	scz.pgs - sle	multiple
-0.002	-0.026	0.022	t	0.873	0.916	scz.pgs - irr	multiple
0.012	-0.015	0.039	t	0.392	0.502	scz.pgs - fore	multiple
-0.001	-0.032	0.030	t	0.957	0.970	scz.pgs - res	multiple
0.015	-0.009	0.039	t	0.207	0.308	scz.pgs - rel	multiple
0.005	-0.018	0.028	t	0.679	0.763	scz.pgs - wor.t	multiple
0.014	-0.010	0.037	t	0.265	0.368	bd.pgs - anx	multiple
0.028	0.003	0.052	t	0.026	0.062	bd.pgs - wor	multiple
0.032	-0.009	0.073	t	0.126	0.215	bd.pgs - psy	multiple
0.014	-0.011	0.039	t	0.280	0.381	bd.pgs - dep	multiple
0.004	-0.022	0.030	t	0.768	0.833	bd.pgs - ina	multiple
0.000	-0.021	0.021	t	0.970	0.970	bd.pgs - tir	multiple
0.003	-0.022	0.029	t	0.797	0.850	bd.pgs - int	multiple
-0.007	-0.033	0.019	t	0.605	0.704	bd.pgs - app	multiple
0.012	-0.033	0.056	t	0.599	0.704	bd.pgs - sui	multiple
0.023	-0.003	0.049	t	0.079	0.154	bd.pgs - con	multiple
0.015	-0.005	0.036	t	0.148	0.225	bd.pgs - sle	multiple
0.014	-0.010	0.038	t	0.264	0.368	bd.pgs - irr	multiple
0.011	-0.015	0.038	t	0.408	0.512	bd.pgs - fore	multiple
0.014	-0.017	0.045	t	0.389	0.502	bd.pgs - res	multiple
0.018	-0.006	0.041	t	0.148	0.225	bd.pgs - rel	multiple
0.023	0.000	0.046	t	0.051	0.106	bd.pgs - wor.t	multiple
0.000	-0.001	0.001	m tot	0.611	0.771	dep.pgs - anx	multiple
0.000	-0.001	0.001	m tot	0.423	0.751	dep.pgs - wor	multiple
0.002	-0.001	0.004	m tot	0.215	0.580	dep.pgs - psy	multiple
0.000	-0.001	0.001	m tot	0.665	0.803	dep.pgs - dep	multiple
0.001	-0.001	0.002	m tot	0.455	0.760	dep.pgs - ina	multiple
0.001	-0.001	0.003	m tot	0.191	0.572	dep.pgs - tir	multiple
0.001	-0.001	0.003	m tot	0.238	0.609	dep.pgs - int	multiple

0.001	-0.001	0.003	m tot	0.343	0.654	dep.pgs - app	multiple
0.001	-0.002	0.003	m tot	0.604	0.771	dep.pgs - sui	multiple
0.000	-0.001	0.001	m tot	0.437	0.757	dep.pgs - con	multiple
0.001	0.000	0.002	m tot	0.261	0.619	dep.pgs - sle	multiple
0.000	-0.001	0.001	m tot	0.477	0.760	dep.pgs - irr	multiple
0.000	-0.001	0.001	m tot	0.824	0.839	dep.pgs - fore	multiple
0.001	-0.001	0.003	m tot	0.336	0.654	dep.pgs - res	multiple
0.000	-0.001	0.001	m tot	0.476	0.760	dep.pgs - rel	multiple
0.000	-0.001	0.001	m tot	0.501	0.760	dep.pgs - wor.t	multiple
-0.001	-0.005	0.003	m tot	0.718	0.820	adhd.pgs - anx	multiple
0.001	-0.003	0.005	m tot	0.534	0.760	adhd.pgs - wor	multiple
0.008	0.001	0.015	m tot	0.020	0.323	adhd.pgs - psy	multiple
0.002	-0.002	0.006	m tot	0.408	0.747	adhd.pgs - dep	multiple
0.003	-0.001	0.008	m tot	0.151	0.548	adhd.pgs - ina	multiple
0.006	0.003	0.010	m tot	0.001	0.064	adhd.pgs - tir	multiple
0.006	0.002	0.011	m tot	0.008	0.265	adhd.pgs - int	multiple
0.006	0.001	0.010	m tot	0.018	0.323	adhd.pgs - app	multiple
0.005	-0.003	0.012	m tot	0.217	0.580	adhd.pgs - sui	multiple
-0.002	-0.007	0.002	m tot	0.312	0.654	adhd.pgs - con	multiple
0.003	0.000	0.007	m tot	0.083	0.433	adhd.pgs - sle	multiple
0.001	-0.003	0.005	m tot	0.529	0.760	adhd.pgs - irr	multiple
0.000	-0.005	0.004	m tot	0.826	0.839	adhd.pgs - fore	multiple
0.005	0.000	0.010	m tot	0.072	0.433	adhd.pgs - res	multiple
0.001	-0.003	0.005	m tot	0.511	0.760	adhd.pgs - rel	multiple
0.001	-0.003	0.004	m tot	0.754	0.824	adhd.pgs - wor.t	multiple
0.000	-0.002	0.001	m tot	0.815	0.839	scz.pgs - anx	multiple
0.000	-0.001	0.002	m tot	0.744	0.824	scz.pgs - wor	multiple
0.003	-0.001	0.006	m tot	0.102	0.465	scz.pgs - psy	multiple
0.001	-0.001	0.002	m tot	0.347	0.654	scz.pgs - dep	multiple
0.001	-0.001	0.003	m tot	0.176	0.563	scz.pgs - ina	multiple
0.002	0.000	0.004	m tot	0.047	0.427	scz.pgs - tir	multiple
0.002	0.000	0.004	m tot	0.070	0.433	scz.pgs - int	multiple
0.002	0.000	0.004	m tot	0.046	0.427	scz.pgs - app	multiple
0.002	-0.001	0.005	m tot	0.197	0.572	scz.pgs - sui	multiple
-0.001	-0.002	0.001	m tot	0.329	0.654	scz.pgs - con	multiple
0.001	0.000	0.003	m tot	0.167	0.561	scz.pgs - sle	multiple

0.000	-0.001	0.002	m tot	0.634	0.781	scz.pgs - irr	multiple
0.000	-0.002	0.001	m tot	0.820	0.839	scz.pgs - fore	multiple
0.002	0.000	0.004	m tot	0.123	0.512	scz.pgs - res	multiple
0.000	-0.001	0.002	m tot	0.614	0.771	scz.pgs - rel	multiple
0.000	-0.001	0.001	m tot	0.992	0.992	scz.pgs - wor.t	multiple
0.000	-0.001	0.002	m tot	0.590	0.771	bd.pgs - anx	multiple
0.000	-0.002	0.001	m tot	0.704	0.820	bd.pgs - wor	multiple
-0.003	-0.006	0.000	m tot	0.088	0.433	bd.pgs - psy	multiple
-0.001	-0.002	0.001	m tot	0.546	0.760	bd.pgs - dep	multiple
-0.001	-0.003	0.001	m tot	0.250	0.615	bd.pgs - ina	multiple
-0.002	-0.005	0.000	m tot	0.034	0.427	bd.pgs - tir	multiple
-0.002	-0.005	0.000	m tot	0.075	0.433	bd.pgs - int	multiple
-0.002	-0.005	0.000	m tot	0.063	0.433	bd.pgs - app	multiple
-0.002	-0.005	0.002	m tot	0.314	0.654	bd.pgs - sui	multiple
0.001	-0.001	0.003	m tot	0.275	0.628	bd.pgs - con	multiple
-0.001	-0.003	0.000	m tot	0.128	0.512	bd.pgs - sle	multiple
-0.001	-0.002	0.001	m tot	0.508	0.760	bd.pgs - irr	multiple
0.000	-0.001	0.002	m tot	0.715	0.820	bd.pgs - fore	multiple
-0.002	-0.004	0.001	m tot	0.154	0.548	bd.pgs - res	multiple
0.000	-0.002	0.001	m tot	0.565	0.769	bd.pgs - rel	multiple
0.000	-0.002	0.001	m tot	0.760	0.824	bd.pgs - wor.t	multiple
0.000	0.000	0.000	m	NA	NA	dep.pgs - mofc - anx	multiple
0.000	0.000	0.000	m	0.520	0.922	dep.pgs - mofc - wor	multiple
0.000	0.000	0.001	m	0.451	0.922	dep.pgs - mofc - psy	multiple
0.000	0.000	0.000	m	NA	NA	dep.pgs - mofc - dep	multiple
0.000	0.000	0.000	m	NA	NA	dep.pgs - mofc - ina	multiple
0.000	0.000	0.001	m	0.439	0.922	dep.pgs - mofc - tir	multiple
0.000	0.000	0.001	m	0.457	0.922	dep.pgs - mofc - int	multiple
0.000	0.000	0.001	m	0.450	0.922	dep.pgs - mofc - app	multiple
0.000	0.000	0.000	m	1.000	1.000	dep.pgs - mofc - sui	multiple
0.000	0.000	0.000	m	NA	NA	dep.pgs - mofc - 0	multiple
0.000	0.000	0.000	m	0.462	0.922	dep.pgs - mofc - anx	multiple
0.000	0.000	0.000	m	0.515	0.922	dep.pgs - mofc - wor	multiple
0.000	0.000	0.000	m	NA	NA	dep.pgs - mofc - psy	multiple
0.000	0.000	0.000	m	0.505	0.922	dep.pgs - mofc - dep	multiple
0.000	0.000	0.000	m	NA	NA	dep.pgs - mofc - ina	multiple

0.000	0.000	0.000	m	NA	NA	dep.pgs - mofc - tir	multiple
0.000	-0.001	0.001	m	0.846	1.000	adhd.pgs - mofc - anx	multiple
0.001	-0.001	0.002	m	0.279	0.922	adhd.pgs - mofc - wor	multiple
0.002	0.000	0.004	m	0.027	0.831	adhd.pgs - mofc - psy	multiple
0.001	-0.001	0.002	m	0.419	0.922	adhd.pgs - mofc - dep	multiple
0.000	-0.001	0.002	m	0.596	0.983	adhd.pgs - mofc - ina	multiple
0.002	0.001	0.003	m	0.003	0.831	adhd.pgs - mofc - tir	multiple
0.001	0.000	0.003	m	0.045	0.831	adhd.pgs - mofc - int	multiple
0.002	0.000	0.003	m	0.024	0.831	adhd.pgs - mofc - app	multiple
0.000	-0.002	0.002	m	1.000	1.000	adhd.pgs - mofc - sui	multiple
-0.001	-0.002	0.001	m	0.436	0.922	adhd.pgs - mofc - 0	multiple
0.001	0.000	0.002	m	0.063	0.898	adhd.pgs - mofc - anx	multiple
0.001	-0.001	0.002	m	0.264	0.922	adhd.pgs - mofc - wor	multiple
0.000	-0.001	0.002	m	0.749	1.000	adhd.pgs - mofc - psy	multiple
0.001	-0.001	0.003	m	0.231	0.922	adhd.pgs - mofc - dep	multiple
0.000	-0.001	0.002	m	0.499	0.922	adhd.pgs - mofc - ina	multiple
0.000	-0.001	0.001	m	0.761	1.000	adhd.pgs - mofc - tir	multiple
0.000	0.000	0.001	m	0.847	1.000	scz.pgs - mofc - anx	multiple
0.000	0.000	0.001	m	0.316	0.922	scz.pgs - mofc - wor	multiple
0.001	0.000	0.002	m	0.089	0.898	scz.pgs - mofc - psy	multiple
0.000	0.000	0.001	m	0.439	0.922	scz.pgs - mofc - dep	multiple
0.000	0.000	0.001	m	0.603	0.990	scz.pgs - mofc - ina	multiple
0.001	0.000	0.001	m	0.047	0.831	scz.pgs - mofc - tir	multiple
0.001	0.000	0.001	m	0.110	0.922	scz.pgs - mofc - int	multiple
0.001	0.000	0.001	m	0.086	0.898	scz.pgs - mofc - app	multiple
0.000	-0.001	0.001	m	1.000	1.000	scz.pgs - mofc - sui	multiple
0.000	-0.001	0.000	m	0.454	0.922	scz.pgs - mofc - 0	multiple
0.000	0.000	0.001	m	0.128	0.922	scz.pgs - mofc - anx	multiple
0.000	0.000	0.001	m	0.303	0.922	scz.pgs - mofc - wor	multiple
0.000	0.000	0.001	m	0.750	1.000	scz.pgs - mofc - psy	multiple
0.000	0.000	0.001	m	0.275	0.922	scz.pgs - mofc - dep	multiple
0.000	0.000	0.001	m	0.512	0.922	scz.pgs - mofc - ina	multiple
0.000	0.000	0.001	m	0.763	1.000	scz.pgs - mofc - tir	multiple
0.000	0.000	0.000	m	NA	NA	bd.pgs - mofc - anx	multiple
0.000	0.000	0.000	m	0.448	0.922	bd.pgs - mofc - wor	multiple
0.000	-0.001	0.000	m	0.337	0.922	bd.pgs - mofc - psy	multiple

0.000	0.000	0.000	m	0.520	0.922	bd.pgs - mofc - dep	multiple
0.000	0.000	0.000	m	0.635	1.000	bd.pgs - mofc - ina	multiple
0.000	-0.001	0.000	m	0.315	0.922	bd.pgs - mofc - tir	multiple
0.000	-0.001	0.000	m	0.347	0.922	bd.pgs - mofc - int	multiple
0.000	-0.001	0.000	m	0.335	0.922	bd.pgs - mofc - app	multiple
0.000	0.000	0.000	m	1.000	1.000	bd.pgs - mofc - sui	multiple
0.000	0.000	0.000	m	0.529	0.922	bd.pgs - mofc - 0	multiple
0.000	-0.001	0.000	m	0.355	0.922	bd.pgs - mofc - anx	multiple
0.000	0.000	0.000	m	0.440	0.922	bd.pgs - mofc - wor	multiple
0.000	0.000	0.000	m	0.759	1.000	bd.pgs - mofc - psy	multiple
0.000	-0.001	0.000	m	0.426	0.922	bd.pgs - mofc - dep	multiple
0.000	0.000	0.000	m	0.568	0.948	bd.pgs - mofc - ina	multiple
0.000	0.000	0.000	m	NA	NA	bd.pgs - mofc - tir	multiple
0.000	0.000	0.000	m	0.815	1.000	dep.pgs - fusi - anx	multiple
0.000	0.000	0.001	m	0.285	0.922	dep.pgs - fusi - wor	multiple
0.001	0.000	0.001	m	0.202	0.922	dep.pgs - fusi - psy	multiple
0.000	0.000	0.001	m	0.509	0.922	dep.pgs - fusi - dep	multiple
0.000	0.000	0.001	m	0.257	0.922	dep.pgs - fusi - ina	multiple
0.000	0.000	0.001	m	0.176	0.922	dep.pgs - fusi - tir	multiple
0.000	0.000	0.001	m	0.157	0.922	dep.pgs - fusi - int	multiple
0.000	0.000	0.000	m	0.908	1.000	dep.pgs - fusi - app	multiple
0.000	0.000	0.001	m	0.281	0.922	dep.pgs - fusi - sui	multiple
0.000	0.000	0.000	m	0.993	1.000	dep.pgs - fusi - 0	multiple
0.000	0.000	0.000	m	0.703	1.000	dep.pgs - fusi - anx	multiple
0.000	0.000	0.000	m	0.970	1.000	dep.pgs - fusi - wor	multiple
0.000	0.000	0.000	m	0.844	1.000	dep.pgs - fusi - psy	multiple
0.000	0.000	0.001	m	0.263	0.922	dep.pgs - fusi - dep	multiple
0.000	0.000	0.000	m	0.476	0.922	dep.pgs - fusi - ina	multiple
0.000	0.000	0.000	m	0.426	0.922	dep.pgs - fusi - tir	multiple
0.000	-0.001	0.001	m	0.814	1.000	adhd.pgs - fusi - anx	multiple
0.001	0.000	0.002	m	0.184	0.922	adhd.pgs - fusi - wor	multiple
0.002	0.000	0.003	m	0.070	0.898	adhd.pgs - fusi - psy	multiple
0.000	-0.001	0.001	m	0.477	0.922	adhd.pgs - fusi - dep	multiple
0.001	0.000	0.002	m	0.143	0.922	adhd.pgs - fusi - ina	multiple
0.001	0.000	0.002	m	0.039	0.831	adhd.pgs - fusi - tir	multiple
0.001	0.000	0.002	m	0.021	0.831	adhd.pgs - fusi - int	multiple

0.000	-0.001	0.001	m	0.908	1.000	adhd.pgs - fusi - app	multiple
0.001	-0.001	0.003	m	0.180	0.922	adhd.pgs - fusi - sui	multiple
0.000	-0.001	0.001	m	0.993	1.000	adhd.pgs - fusi - 0	multiple
0.000	-0.001	0.001	m	0.696	1.000	adhd.pgs - fusi - anx	multiple
0.000	-0.001	0.001	m	0.970	1.000	adhd.pgs - fusi - wor	multiple
0.000	-0.001	0.001	m	0.843	1.000	adhd.pgs - fusi - psy	multiple
0.001	0.000	0.002	m	0.153	0.922	adhd.pgs - fusi - dep	multiple
0.000	-0.001	0.001	m	0.438	0.922	adhd.pgs - fusi - ina	multiple
0.000	0.000	0.001	m	0.375	0.922	adhd.pgs - fusi - tir	multiple
0.000	0.000	0.000	m	NA	NA	scz.pgs - fusi - anx	multiple
0.000	0.000	0.000	m	0.673	1.000	scz.pgs - fusi - wor	multiple
0.000	-0.001	0.001	m	0.666	1.000	scz.pgs - fusi - psy	multiple
0.000	0.000	0.000	m	NA	NA	scz.pgs - fusi - dep	multiple
0.000	0.000	0.000	m	0.670	1.000	scz.pgs - fusi - ina	multiple
0.000	0.000	0.001	m	0.664	1.000	scz.pgs - fusi - tir	multiple
0.000	0.000	0.001	m	0.662	1.000	scz.pgs - fusi - int	multiple
0.000	0.000	0.000	m	NA	NA	scz.pgs - fusi - app	multiple
0.000	0.000	0.001	m	0.673	1.000	scz.pgs - fusi - sui	multiple
0.000	0.000	0.000	m	NA	NA	scz.pgs - fusi - 0	multiple
0.000	0.000	0.000	m	NA	NA	scz.pgs - fusi - anx	multiple
0.000	0.000	0.000	m	NA	NA	scz.pgs - fusi - wor	multiple
0.000	0.000	0.000	m	NA	NA	scz.pgs - fusi - psy	multiple
0.000	0.000	0.000	m	0.671	1.000	scz.pgs - fusi - dep	multiple
0.000	0.000	0.000	m	NA	NA	scz.pgs - fusi - ina	multiple
0.000	0.000	0.000	m	NA	NA	scz.pgs - fusi - tir	multiple
0.000	0.000	0.000	m	NA	NA	bd.pgs - fusi - anx	multiple
0.000	-0.001	0.000	m	0.377	0.922	bd.pgs - fusi - wor	multiple
0.000	-0.001	0.000	m	0.323	0.922	bd.pgs - fusi - psy	multiple
0.000	0.000	0.000	m	0.542	0.928	bd.pgs - fusi - dep	multiple
0.000	-0.001	0.000	m	0.358	0.922	bd.pgs - fusi - ina	multiple
0.000	-0.001	0.000	m	0.306	0.922	bd.pgs - fusi - tir	multiple
0.000	-0.001	0.000	m	0.293	0.922	bd.pgs - fusi - int	multiple
0.000	0.000	0.000	m	0.908	1.000	bd.pgs - fusi - app	multiple
0.000	-0.001	0.000	m	0.376	0.922	bd.pgs - fusi - sui	multiple
0.000	0.000	0.000	m	0.993	1.000	bd.pgs - fusi - 0	multiple
0.000	0.000	0.000	m	NA	NA	bd.pgs - fusi - anx	multiple

0.000	0.000	0.000	m	NA	NA	bd.pgs - fusi - wor	multiple
0.000	0.000	0.000	m	0.845	1.000	bd.pgs - fusi - psy	multiple
0.000	-0.001	0.000	m	0.363	0.922	bd.pgs - fusi - dep	multiple
0.000	0.000	0.000	m	0.517	0.922	bd.pgs - fusi - ina	multiple
0.000	0.000	0.000	m	0.478	0.922	bd.pgs - fusi - tir	multiple
0.000	0.000	0.000	m	0.572	0.948	dep.pgs - ins - anx	multiple
0.000	0.000	0.000	m	0.851	1.000	dep.pgs - ins - wor	multiple
0.000	0.000	0.001	m	0.240	0.922	dep.pgs - ins - psy	multiple
0.000	0.000	0.000	m	0.741	1.000	dep.pgs - ins - dep	multiple
0.000	0.000	0.001	m	0.451	0.922	dep.pgs - ins - ina	multiple
0.000	0.000	0.001	m	0.159	0.922	dep.pgs - ins - tir	multiple
0.000	0.000	0.001	m	0.253	0.922	dep.pgs - ins - int	multiple
0.000	0.000	0.001	m	0.201	0.922	dep.pgs - ins - app	multiple
0.000	0.000	0.001	m	0.460	0.922	dep.pgs - ins - sui	multiple
0.000	-0.001	0.000	m	0.373	0.922	dep.pgs - ins - 0	multiple
0.000	0.000	0.000	m	0.348	0.922	dep.pgs - ins - anx	multiple
0.000	0.000	0.000	m	0.492	0.922	dep.pgs - ins - wor	multiple
0.000	0.000	0.000	m	0.971	1.000	dep.pgs - ins - psy	multiple
0.000	0.000	0.001	m	0.385	0.922	dep.pgs - ins - dep	multiple
0.000	0.000	0.000	m	0.746	1.000	dep.pgs - ins - ina	multiple
0.000	0.000	0.000	m	0.777	1.000	dep.pgs - ins - tir	multiple
0.000	-0.002	0.001	m	0.548	0.932	adhd.pgs - ins - anx	multiple
0.000	-0.001	0.001	m	0.850	1.000	adhd.pgs - ins - wor	multiple
0.002	0.000	0.004	m	0.098	0.900	adhd.pgs - ins - psy	multiple
0.000	-0.001	0.002	m	0.736	1.000	adhd.pgs - ins - dep	multiple
0.001	-0.001	0.002	m	0.399	0.922	adhd.pgs - ins - ina	multiple
0.002	0.000	0.003	m	0.009	0.831	adhd.pgs - ins - tir	multiple
0.001	0.000	0.002	m	0.117	0.922	adhd.pgs - ins - int	multiple
0.001	0.000	0.003	m	0.047	0.831	adhd.pgs - ins - app	multiple
0.001	-0.001	0.003	m	0.410	0.922	adhd.pgs - ins - sui	multiple
-0.001	-0.002	0.001	m	0.293	0.922	adhd.pgs - ins - 0	multiple
0.001	0.000	0.002	m	0.256	0.922	adhd.pgs - ins - anx	multiple
0.000	-0.001	0.002	m	0.451	0.922	adhd.pgs - ins - wor	multiple
0.000	-0.001	0.001	m	0.971	1.000	adhd.pgs - ins - psy	multiple
0.001	-0.001	0.002	m	0.309	0.922	adhd.pgs - ins - dep	multiple
0.000	-0.001	0.001	m	0.741	1.000	adhd.pgs - ins - ina	multiple

0.000	-0.001	0.001	m	0.773	1.000	adhd.pgs - ins - tir	multiple
0.000	0.000	0.000	m	0.571	0.948	scz.pgs - ins - anx	multiple
0.000	0.000	0.000	m	0.851	1.000	scz.pgs - ins - wor	multiple
0.000	0.000	0.001	m	0.238	0.922	scz.pgs - ins - psy	multiple
0.000	0.000	0.000	m	0.741	1.000	scz.pgs - ins - dep	multiple
0.000	0.000	0.001	m	0.450	0.922	scz.pgs - ins - ina	multiple
0.000	0.000	0.001	m	0.156	0.922	scz.pgs - ins - tir	multiple
0.000	0.000	0.001	m	0.251	0.922	scz.pgs - ins - int	multiple
0.000	0.000	0.001	m	0.198	0.922	scz.pgs - ins - app	multiple
0.000	0.000	0.001	m	0.459	0.922	scz.pgs - ins - sui	multiple
0.000	-0.001	0.000	m	0.372	0.922	scz.pgs - ins - 0	multiple
0.000	0.000	0.001	m	0.346	0.922	scz.pgs - ins - anx	multiple
0.000	0.000	0.000	m	0.492	0.922	scz.pgs - ins - wor	multiple
0.000	0.000	0.000	m	0.971	1.000	scz.pgs - ins - psy	multiple
0.000	0.000	0.001	m	0.383	0.922	scz.pgs - ins - dep	multiple
0.000	0.000	0.000	m	0.746	1.000	scz.pgs - ins - ina	multiple
0.000	0.000	0.000	m	0.777	1.000	scz.pgs - ins - tir	multiple
0.000	-0.001	0.001	m	0.551	0.933	bd.pgs - ins - anx	multiple
0.000	-0.001	0.001	m	0.850	1.000	bd.pgs - ins - wor	multiple
-0.001	-0.003	0.000	m	0.118	0.922	bd.pgs - ins - psy	multiple
0.000	-0.001	0.001	m	0.736	1.000	bd.pgs - ins - dep	multiple
0.000	-0.001	0.001	m	0.406	0.922	bd.pgs - ins - ina	multiple
-0.001	-0.002	0.000	m	0.022	0.831	bd.pgs - ins - tir	multiple
-0.001	-0.002	0.000	m	0.136	0.922	bd.pgs - ins - int	multiple
-0.001	-0.002	0.000	m	0.066	0.898	bd.pgs - ins - app	multiple
-0.001	-0.002	0.001	m	0.417	0.922	bd.pgs - ins - sui	multiple
0.000	0.000	0.001	m	0.304	0.922	bd.pgs - ins - 0	multiple
0.000	-0.001	0.000	m	0.269	0.922	bd.pgs - ins - anx	multiple
0.000	-0.001	0.001	m	0.457	0.922	bd.pgs - ins - wor	multiple
0.000	-0.001	0.001	m	0.971	1.000	bd.pgs - ins - psy	multiple
-0.001	-0.002	0.001	m	0.319	0.922	bd.pgs - ins - dep	multiple
0.000	-0.001	0.001	m	0.742	1.000	bd.pgs - ins - ina	multiple
0.000	-0.001	0.001	m	0.774	1.000	bd.pgs - ins - tir	multiple
0.000	0.000	0.000	m	NA	NA	dep.pgs - hip - anx	multiple
0.000	0.000	0.000	m	NA	NA	dep.pgs - hip - wor	multiple
0.000	0.000	0.000	m	0.780	1.000	dep.pgs - hip - psy	multiple

0.000	0.000	0.000	m	0.777	1.000	dep.pgs - hip - dep	multiple
0.000	-0.001	0.000	m	0.775	1.000	dep.pgs - hip - ina	multiple
0.000	0.000	0.000	m	0.776	1.000	dep.pgs - hip - tir	multiple
0.000	-0.001	0.000	m	0.775	1.000	dep.pgs - hip - int	multiple
0.000	-0.001	0.000	m	0.775	1.000	dep.pgs - hip - app	multiple
0.000	-0.001	0.001	m	0.774	1.000	dep.pgs - hip - sui	multiple
0.000	0.000	0.000	m	NA	NA	dep.pgs - hip - 0	multiple
0.000	0.000	0.000	m	NA	NA	dep.pgs - hip - anx	multiple
0.000	0.000	0.000	m	NA	NA	dep.pgs - hip - wor	multiple
0.000	0.000	0.000	m	NA	NA	dep.pgs - hip - psy	multiple
0.000	-0.001	0.000	m	0.776	1.000	dep.pgs - hip - dep	multiple
0.000	0.000	0.000	m	NA	NA	dep.pgs - hip - ina	multiple
0.000	0.000	0.000	m	NA	NA	dep.pgs - hip - tir	multiple
0.000	-0.001	0.001	m	0.887	1.000	adhd.pgs - hip - anx	multiple
0.000	-0.001	0.001	m	0.618	1.000	adhd.pgs - hip - wor	multiple
0.001	-0.001	0.002	m	0.265	0.922	adhd.pgs - hip - psy	multiple
0.001	0.000	0.001	m	0.169	0.922	adhd.pgs - hip - dep	multiple
0.001	0.000	0.002	m	0.037	0.831	adhd.pgs - hip - ina	multiple
0.001	0.000	0.001	m	0.094	0.898	adhd.pgs - hip - tir	multiple
0.001	0.000	0.002	m	0.042	0.831	adhd.pgs - hip - int	multiple
0.001	0.000	0.002	m	0.052	0.831	adhd.pgs - hip - app	multiple
0.002	0.000	0.004	m	0.016	0.831	adhd.pgs - hip - sui	multiple
0.000	-0.001	0.001	m	0.690	1.000	adhd.pgs - hip - 0	multiple
0.000	-0.001	0.001	m	0.998	1.000	adhd.pgs - hip - anx	multiple
0.000	-0.001	0.000	m	0.446	0.922	adhd.pgs - hip - wor	multiple
0.000	-0.001	0.001	m	0.976	1.000	adhd.pgs - hip - psy	multiple
0.001	0.000	0.002	m	0.080	0.898	adhd.pgs - hip - dep	multiple
0.000	-0.001	0.001	m	0.940	1.000	adhd.pgs - hip - ina	multiple
0.000	-0.001	0.000	m	0.391	0.922	adhd.pgs - hip - tir	multiple
0.000	0.000	0.001	m	0.887	1.000	scz.pgs - hip - anx	multiple
0.000	-0.001	0.000	m	0.622	1.000	scz.pgs - hip - wor	multiple
0.001	0.000	0.001	m	0.290	0.922	scz.pgs - hip - psy	multiple
0.000	0.000	0.001	m	0.202	0.922	scz.pgs - hip - dep	multiple
0.001	0.000	0.002	m	0.076	0.898	scz.pgs - hip - ina	multiple
0.000	0.000	0.001	m	0.134	0.922	scz.pgs - hip - tir	multiple
0.001	0.000	0.001	m	0.081	0.898	scz.pgs - hip - int	multiple

0.001	0.000	0.001	m	0.092	0.898	scz.pgs - hip - app	multiple
0.001	0.000	0.003	m	0.049	0.831	scz.pgs - hip - sui	multiple
0.000	-0.001	0.000	m	0.692	1.000	scz.pgs - hip - 0	multiple
0.000	0.000	0.000	m	0.998	1.000	scz.pgs - hip - anx	multiple
0.000	-0.001	0.000	m	0.457	0.922	scz.pgs - hip - wor	multiple
0.000	-0.001	0.001	m	0.976	1.000	scz.pgs - hip - psy	multiple
0.001	0.000	0.002	m	0.120	0.922	scz.pgs - hip - dep	multiple
0.000	-0.001	0.000	m	0.940	1.000	scz.pgs - hip - ina	multiple
0.000	-0.001	0.000	m	0.405	0.922	scz.pgs - hip - tir	multiple
0.000	0.000	0.000	m	NA	NA	bd.pgs - hip - anx	multiple
0.000	0.000	0.000	m	0.648	1.000	bd.pgs - hip - wor	multiple
0.000	-0.001	0.000	m	0.427	0.922	bd.pgs - hip - psy	multiple
0.000	-0.001	0.000	m	0.382	0.922	bd.pgs - hip - dep	multiple
0.000	-0.001	0.000	m	0.320	0.922	bd.pgs - hip - ina	multiple
0.000	-0.001	0.000	m	0.348	0.922	bd.pgs - hip - tir	multiple
0.000	-0.001	0.000	m	0.322	0.922	bd.pgs - hip - int	multiple
0.000	-0.001	0.000	m	0.327	0.922	bd.pgs - hip - app	multiple
-0.001	-0.002	0.001	m	0.305	0.922	bd.pgs - hip - sui	multiple
0.000	0.000	0.000	m	0.707	1.000	bd.pgs - hip - 0	multiple
0.000	0.000	0.000	m	NA	NA	bd.pgs - hip - anx	multiple
0.000	0.000	0.000	m	0.527	0.922	bd.pgs - hip - wor	multiple
0.000	0.000	0.000	m	0.976	1.000	bd.pgs - hip - psy	multiple
0.000	-0.001	0.000	m	0.341	0.922	bd.pgs - hip - dep	multiple
0.000	0.000	0.000	m	NA	NA	bd.pgs - hip - ina	multiple
0.000	0.000	0.000	m	0.494	0.922	bd.pgs - hip - tir	multiple
0.000	0.000	0.000	m	0.536	0.922	dep.pgs - cing - anx	multiple
0.000	0.000	0.000	m	0.975	1.000	dep.pgs - cing - wor	multiple
0.000	0.000	0.001	m	0.303	0.922	dep.pgs - cing - psy	multiple
0.000	0.000	0.000	m	0.926	1.000	dep.pgs - cing - dep	multiple
0.000	0.000	0.000	m	0.531	0.922	dep.pgs - cing - ina	multiple
0.000	0.000	0.001	m	0.256	0.922	dep.pgs - cing - tir	multiple
0.000	0.000	0.001	m	0.285	0.922	dep.pgs - cing - int	multiple
0.000	0.000	0.001	m	0.279	0.922	dep.pgs - cing - app	multiple
0.000	0.000	0.000	m	0.815	1.000	dep.pgs - cing - sui	multiple
0.000	-0.001	0.000	m	0.366	0.922	dep.pgs - cing - 0	multiple
0.000	0.000	0.001	m	0.265	0.922	dep.pgs - cing - anx	multiple

0.000	0.000	0.000	m	0.525	0.922	dep.pgs - cing - wor	multiple
0.000	-0.001	0.000	m	0.388	0.922	dep.pgs - cing - psy	multiple
0.000	0.000	0.001	m	0.330	0.922	dep.pgs - cing - dep	multiple
0.000	0.000	0.000	m	0.563	0.947	dep.pgs - cing - ina	multiple
0.000	0.000	0.000	m	NA	NA	dep.pgs - cing - tir	multiple
0.000	-0.002	0.001	m	0.478	0.922	adhd.pgs - cing - anx	multiple
0.000	-0.001	0.001	m	0.975	1.000	adhd.pgs - cing - wor	multiple
0.002	0.000	0.004	m	0.074	0.898	adhd.pgs - cing - psy	multiple
0.000	-0.001	0.001	m	0.926	1.000	adhd.pgs - cing - dep	multiple
0.000	-0.001	0.002	m	0.471	0.922	adhd.pgs - cing - ina	multiple
0.001	0.000	0.003	m	0.009	0.831	adhd.pgs - cing - tir	multiple
0.001	0.000	0.003	m	0.043	0.831	adhd.pgs - cing - int	multiple
0.001	0.000	0.003	m	0.035	0.831	adhd.pgs - cing - app	multiple
0.000	-0.002	0.002	m	0.812	1.000	adhd.pgs - cing - sui	multiple
-0.001	-0.002	0.000	m	0.195	0.922	adhd.pgs - cing - 0	multiple
0.001	0.000	0.002	m	0.017	0.831	adhd.pgs - cing - anx	multiple
0.000	-0.001	0.002	m	0.462	0.922	adhd.pgs - cing - wor	multiple
-0.001	-0.002	0.001	m	0.236	0.922	adhd.pgs - cing - psy	multiple
0.001	0.000	0.003	m	0.124	0.922	adhd.pgs - cing - dep	multiple
0.000	-0.001	0.002	m	0.515	0.922	adhd.pgs - cing - ina	multiple
0.000	-0.001	0.001	m	0.743	1.000	adhd.pgs - cing - tir	multiple
0.000	-0.001	0.000	m	0.502	0.922	scz.pgs - cing - anx	multiple
0.000	0.000	0.000	m	0.975	1.000	scz.pgs - cing - wor	multiple
0.001	0.000	0.001	m	0.179	0.922	scz.pgs - cing - psy	multiple
0.000	0.000	0.000	m	0.926	1.000	scz.pgs - cing - dep	multiple
0.000	0.000	0.001	m	0.496	0.922	scz.pgs - cing - ina	multiple
0.000	0.000	0.001	m	0.108	0.922	scz.pgs - cing - tir	multiple
0.000	0.000	0.001	m	0.151	0.922	scz.pgs - cing - int	multiple
0.000	0.000	0.001	m	0.143	0.922	scz.pgs - cing - app	multiple
0.000	-0.001	0.001	m	0.813	1.000	scz.pgs - cing - sui	multiple
0.000	-0.001	0.000	m	0.274	0.922	scz.pgs - cing - 0	multiple
0.000	0.000	0.001	m	0.121	0.922	scz.pgs - cing - anx	multiple
0.000	0.000	0.001	m	0.489	0.922	scz.pgs - cing - wor	multiple
0.000	-0.001	0.000	m	0.305	0.922	scz.pgs - cing - psy	multiple
0.000	0.000	0.001	m	0.220	0.922	scz.pgs - cing - dep	multiple
0.000	0.000	0.001	m	0.535	0.922	scz.pgs - cing - ina	multiple

0.000	0.000	0.000	m	0.746	1.000	scz.pgs - cing - tir	multiple
0.000	0.000	0.001	m	0.490	0.922	bd.pgs - cing - anx	multiple
0.000	-0.001	0.001	m	0.975	1.000	bd.pgs - cing - wor	multiple
-0.001	-0.002	0.000	m	0.126	0.922	bd.pgs - cing - psy	multiple
0.000	-0.001	0.001	m	0.926	1.000	bd.pgs - cing - dep	multiple
0.000	-0.001	0.000	m	0.483	0.922	bd.pgs - cing - ina	multiple
-0.001	-0.001	0.000	m	0.050	0.831	bd.pgs - cing - tir	multiple
-0.001	-0.001	0.000	m	0.095	0.898	bd.pgs - cing - int	multiple
-0.001	-0.001	0.000	m	0.086	0.898	bd.pgs - cing - app	multiple
0.000	-0.001	0.001	m	0.813	1.000	bd.pgs - cing - sui	multiple
0.000	0.000	0.001	m	0.235	0.922	bd.pgs - cing - 0	multiple
-0.001	-0.001	0.000	m	0.063	0.898	bd.pgs - cing - anx	multiple
0.000	-0.001	0.000	m	0.475	0.922	bd.pgs - cing - wor	multiple
0.000	0.000	0.001	m	0.271	0.922	bd.pgs - cing - psy	multiple
-0.001	-0.001	0.000	m	0.173	0.922	bd.pgs - cing - dep	multiple
0.000	-0.001	0.000	m	0.524	0.922	bd.pgs - cing - ina	multiple
0.000	-0.001	0.000	m	0.745	1.000	bd.pgs - cing - tir	multiple

Supplementary Table 2: 'Total scores' mediation analysis results

Estimate	Lower CI	Upper CI	p-value	Adjusted p-value	Path type	Label
-0.017	-0.033	0.000	0.051	0.105	b	mOFC - Total Depression
-0.002	-0.018	0.015	0.844	0.844	b	Fusiform - Total Depression
-0.002	-0.018	0.015	0.837	0.844	b	Insula - Total Depression
-0.013	-0.030	0.004	0.133	0.214	b	Hippocampus - Total Depression
-0.008	-0.024	0.009	0.357	0.432	b	Cingulate - Total Depression
0.054	0.038	0.069	0.000	0.000	c	Depression PGS - Total Depression
0.039	0.024	0.055	0.000	0.000	c	ADHD PGS - Total Depression
0.018	0.001	0.034	0.033	0.079	c	Schizophrenia PGS - Total Depression
0.009	-0.008	0.025	0.304	0.384	c	Bipolar disorder PGS - Total Depression
0.054	0.038	0.070	0.000	0.000	t	Depression PGS - Total Depression
0.041	0.026	0.057	0.000	0.000	t	ADHD PGS - Total Depression
0.018	0.002	0.035	0.026	0.034	t	Schizophrenia PGS - Total Depression
0.008	-0.008	0.025	0.332	0.332	t	Bipolar disorder PGS - Total Depression
0.000	-0.001	0.001	0.583	0.583	m tot	Depression PGS - Total Depression
0.002	-0.001	0.004	0.214	0.428	m tot	ADHD PGS - Total Depression
0.001	0.000	0.002	0.158	0.428	m tot	Schizophrenia PGS - Total Depression
-0.001	-0.002	0.001	0.385	0.514	m tot	Bipolar disorder PGS - Total Depression
-0.013	-0.029	0.004	0.134	0.228	b	mOFC - Total Anxiety
-0.009	-0.026	0.008	0.303	0.399	b	Fusiform - Total Anxiety
0.003	-0.013	0.020	0.687	0.737	b	Insula - Total Anxiety
0.003	-0.014	0.019	0.740	0.755	b	Hippocampus - Total Anxiety
0.004	-0.012	0.021	0.598	0.694	b	Cingulate - Total Anxiety
0.044	0.028	0.060	0.000	0.000	c	Depression PGS - Total Anxiety
0.027	0.011	0.043	0.001	0.004	c	ADHD PGS - Total Anxiety
0.007	-0.009	0.023	0.424	0.513	c	Schizophrenia PGS - Total Anxiety
0.017	0.000	0.034	0.046	0.102	c	Bipolar disorder PGS - Total Anxiety
0.044	0.028	0.060	0.000	0.000	t	Depression PGS - Total Anxiety
0.027	0.011	0.043	0.001	0.001	t	ADHD PGS - Total Anxiety
0.007	-0.009	0.023	0.415	0.415	t	Schizophrenia PGS - Total Anxiety
0.017	0.000	0.034	0.044	0.059	t	Bipolar disorder PGS - Total Anxiety
0.000	0.000	0.001	0.694	0.946	m tot	Depression PGS - Total Anxiety
0.000	-0.002	0.003	0.722	0.946	m tot	ADHD PGS - Total Anxiety
0.000	-0.001	0.001	0.819	0.946	m tot	Schizophrenia PGS - Total Anxiety
0.000	-0.001	0.001	0.946	0.946	m tot	Bipolar disorder PGS - Total Anxiety

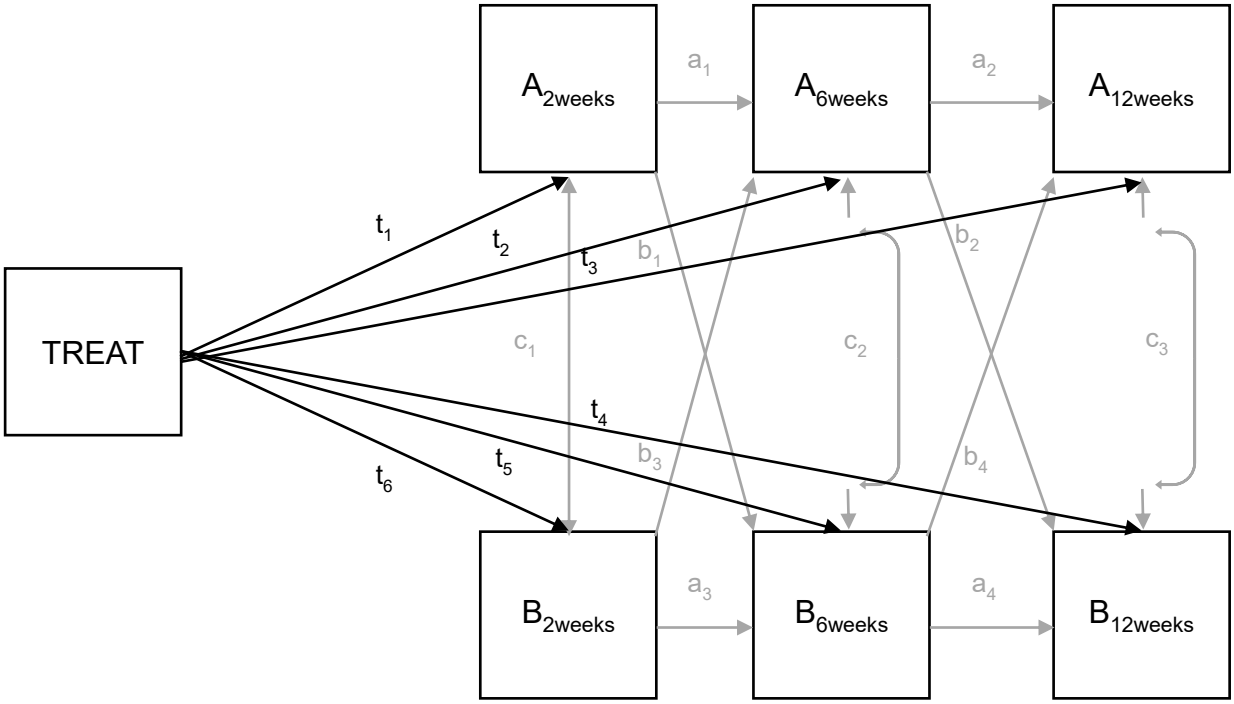
Supplementary Table 3: Simple correlations between symptom outcomes and regional brain volumes.

Symptom	Brain area	r	p-value	Lower CI	Upper CI	Adjusted p-value
anx	mofc	-0.037	0.000	-0.053	-0.020	0.000
anx	fusi	-0.036	0.000	-0.052	-0.020	0.000
anx	ins	-0.050	0.000	-0.066	-0.034	0.000
anx	hip	-0.015	0.061	-0.030	0.001	0.109
anx	cing	-0.027	0.001	-0.043	-0.010	0.004
wor	mofc	-0.045	0.000	-0.060	-0.029	0.000
wor	fusi	-0.047	0.000	-0.063	-0.031	0.000
wor	ins	-0.055	0.000	-0.071	-0.039	0.000
wor	hip	-0.013	0.095	-0.029	0.002	0.158
wor	cing	-0.033	0.000	-0.049	-0.017	0.000
psy	mofc	-0.019	0.020	-0.036	-0.003	0.041
psy	fusi	-0.013	0.103	-0.028	0.003	0.165
psy	ins	-0.016	0.045	-0.033	0.000	0.087
psy	hip	-0.005	0.512	-0.021	0.010	0.602
psy	cing	-0.013	0.118	-0.028	0.003	0.180
dep	mofc	-0.008	0.334	-0.025	0.009	0.418
dep	fusi	-0.007	0.412	-0.023	0.009	0.499
dep	ins	-0.021	0.015	-0.038	-0.004	0.032
dep	hip	0.005	0.549	-0.011	0.021	0.637
dep	cing	-0.004	0.604	-0.020	0.012	0.680
ina	mofc	-0.007	0.369	-0.023	0.009	0.454
ina	fusi	-0.011	0.181	-0.027	0.005	0.245
ina	ins	-0.026	0.002	-0.042	-0.009	0.005
ina	hip	0.002	0.848	-0.014	0.017	0.910
ina	cing	-0.009	0.259	-0.025	0.007	0.335
tir	mofc	-0.056	0.000	-0.072	-0.039	0.000
tir	fusi	-0.044	0.000	-0.060	-0.028	0.000
tir	ins	-0.065	0.000	-0.082	-0.049	0.000
tir	hip	-0.023	0.008	-0.041	-0.006	0.018
tir	cing	-0.050	0.000	-0.066	-0.034	0.000
int	mofc	-0.015	0.072	-0.031	0.001	0.126
int	fusi	-0.013	0.099	-0.029	0.002	0.162
int	ins	-0.023	0.005	-0.040	-0.007	0.012
int	hip	0.002	0.851	-0.015	0.018	0.910
int	cing	-0.015	0.055	-0.031	0.000	0.100
app	mofc	-0.041	0.000	-0.058	-0.025	0.000
app	fusi	-0.022	0.006	-0.038	-0.006	0.014
app	ins	-0.062	0.000	-0.079	-0.046	0.000
app	hip	-0.011	0.192	-0.027	0.005	0.256

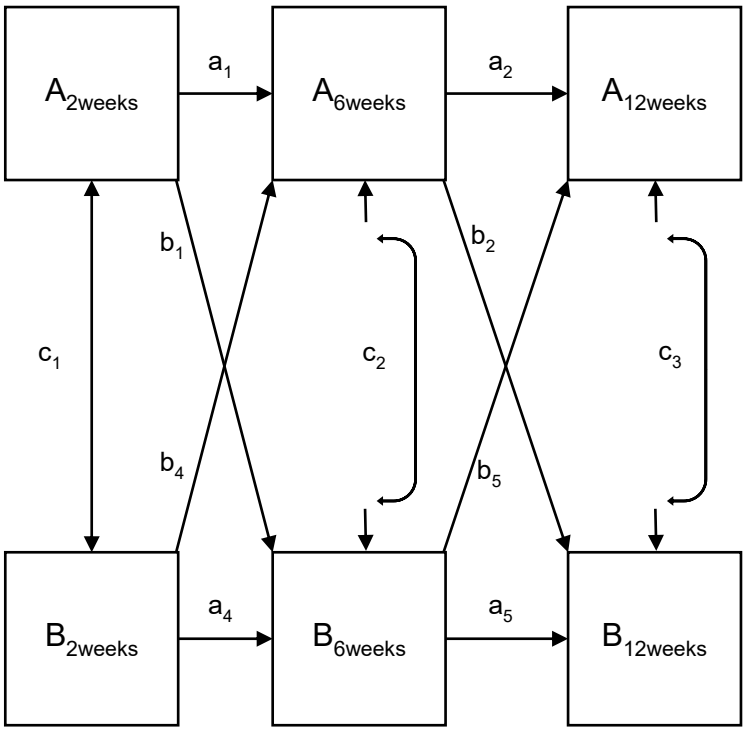
app	cing	-0.038	0.000	-0.055	-0.022	0.000
sui	mofc	-0.001	0.930	-0.016	0.015	0.962
sui	fusi	-0.006	0.495	-0.022	0.010	0.591
sui	ins	-0.010	0.237	-0.026	0.006	0.311
sui	hip	-0.012	0.119	-0.028	0.003	0.180
sui	cing	-0.004	0.629	-0.020	0.012	0.699
con	mofc	0.012	0.141	-0.004	0.028	0.209
con	fusi	0.013	0.120	-0.003	0.029	0.180
con	ins	0.000	0.958	-0.016	0.015	0.962
con	hip	0.027	0.001	0.011	0.043	0.002
con	cing	0.016	0.050	0.000	0.031	0.094
sle	mofc	-0.054	0.000	-0.071	-0.038	0.000
sle	fusi	-0.042	0.000	-0.058	-0.026	0.000
sle	ins	-0.069	0.000	-0.085	-0.052	0.000
sle	hip	-0.018	0.038	-0.034	-0.001	0.077
sle	cing	-0.054	0.000	-0.070	-0.038	0.000
irr	mofc	-0.001	0.893	-0.018	0.016	0.940
irr	fusi	0.012	0.173	-0.005	0.029	0.239
irr	ins	-0.012	0.172	-0.028	0.005	0.239
irr	hip	0.031	0.000	0.014	0.047	0.001
irr	cing	0.000	0.962	-0.017	0.018	0.962
fore	mofc	-0.029	0.000	-0.046	-0.013	0.001
fore	fusi	-0.027	0.001	-0.043	-0.011	0.002
fore	ins	-0.043	0.000	-0.058	-0.027	0.000
fore	hip	-0.004	0.591	-0.021	0.012	0.676
fore	cing	-0.016	0.048	-0.033	0.000	0.092
res	mofc	-0.011	0.172	-0.027	0.005	0.239
res	fusi	-0.011	0.172	-0.027	0.005	0.239
res	ins	-0.023	0.005	-0.039	-0.007	0.012
res	hip	0.002	0.853	-0.014	0.018	0.910
res	cing	-0.013	0.090	-0.029	0.002	0.153
rel	mofc	-0.027	0.001	-0.044	-0.011	0.003
rel	fusi	-0.026	0.001	-0.042	-0.010	0.004
rel	ins	-0.045	0.000	-0.062	-0.029	0.000
rel	hip	0.000	0.952	-0.016	0.015	0.962
rel	cing	-0.025	0.002	-0.041	-0.009	0.005
wor.t	mofc	-0.037	0.000	-0.053	-0.022	0.000
wor.t	fusi	-0.041	0.000	-0.057	-0.025	0.000
wor.t	ins	-0.054	0.000	-0.070	-0.038	0.000
wor.t	hip	-0.008	0.315	-0.024	0.008	0.400
wor.t	cing	-0.033	0.000	-0.050	-0.017	0.000

Appendix C – Supplementary Material for Chapter 4

Supplementary Figures



Supplementary Figure 1: Schematic representation of the cross-lagged panel model used to derive network edges in Figure 4.3 (a-b).
In this model, treatment allocation is a time-invariant predictor ("TREAT"), predicting individual symptoms (observed variables) at 2-, 6- and 12-weeks follow-ups. In this example, A and B are individual symptoms, paths marked 't' are regression coefficients between treatment allocation and symptoms, 'a' paths indicate autoregressive relationships and 'c' paths indicate cross-lagged relationships. The full model includes 21 symptoms.



Supplementary Figure 2: Schematic representation of the cross-lagged panel model used to derive networks in Model 1-2.

In this example, A and B are individual symptoms (observed variables), paths marked ‘a’ indicate autoregressive relationships and ‘c’ paths indicate cross-lagged relationships. The full model includes 21 symptoms. Treatment and placebo groups were compared with multi-group modelling by fixing all paths to be equal between groups at the same time (Model 1). Comparisons of edges were then carried out by comparing a model with equal edges between groups (Model 1) to a model where edges were free to vary between groups (Models 2).

Supplementary Tables

Supplementary Table 1: Demographic characteristics of the sample (size and percentage of the total sample) and means and standard deviations of age, total scores on PHQ-9 and GAD-7.

Characteristic	**Sertraline**	**Placebo**
	N = 324	N = 329
Sex		
Male	121 (37%)	148 (45%)
Female	203 (63%)	181 (55%)
Age	39.67 (15.38)	39.74 (14.56)
Ethnic Group		
White	294 (91%)	285 (87%)
Ethnic Minority	29 (9.0%)	44 (13%)
Site		
Bristol	131 (40%)	134 (41%)
Liverpool	58 (18%)	58 (18%)
York	66 (20%)	64 (19%)
London	69 (21%)	73 (22%)
Antidepressants used in the past	191 (59%)	200 (61%)
Depressed in the past	259 (80%)	263 (80%)
Highest qualifications		
Higher degree (e.g. M.A., PGCE) or equivalent	39 (12%)	42 (13%)
Degree (e.g. B. Sc., B.A.) or equivalent	67 (21%)	82 (25%)
Diploma (e.g. HND, NVQ, level 3) or equivalent	62 (19%)	61 (19%)
A-level or equivalent	48 (15%)	49 (15%)
GCSE, O-level, CSE or equivalent	76 (24%)	69 (21%)
Other qualifications	16 (5.0%)	8 (2.4%)
No qualifications	15 (4.6%)	18 (5.5%)
Marital Status		
Married/Living as married	116 (36%)	139 (42%)
Single	152 (47%)	144 (44%)
Separated	14 (4.3%)	14 (4.3%)
Divorced	30 (9.3%)	25 (7.6%)
Widowed	11 (3.4%)	7 (2.1%)
PHQ-9 total score	11.80 (5.89)	12.20 (5.71)
GAD-7 total score	9.44 (5.39)	9.42 (5.17)

Supplementary Table 2: Network nodes used in network estimation with brief description. Nodes were derived by combining questionnaire items from PHQ-9, GAD-7 and BDI-II.

Network node	Description	Questionnaire item(s)
BAD	Feeling bad about oneself	**PHQ-6** ("Feeling bad about yourself — or that you are a failure or have let yourself or your family down")
ANX	Feeling nervous or anxious	**GAD-1** ("Feeling nervous, anxious, or on edge")
AFR	Feeling afraid	**GAD-7** ("Feeling afraid, as if something awful might happen")
FAI	Past failure	**BDI-3** (Past failure, from "I do not feel like a failure" to "I feel like I am a total failure as a person")
GUI	Guilty feelings	**BDI -5** (Guilty feelings, from "I don't feel particularly guilty" to "I feel guilty all of the time")
PUN	Punishment feelings	**BDI -6** (Punishment feelings, from "I don't feel I am being punished" to "I feel I am being punished")
CRY	Crying	**BDI -10** (Crying, from "I don't cry any more than I used to" to "I feel like crying, but I can't")
IND	Indecisiveness	**BDI -13** (Indecisiveness, from "I make decisions about as well as ever" to "I have trouble making any decisions")
LIB	Loss of interest in sex	**BDI -21** (Loss of interest in sex, from "I have not noticed any recent change in my interest in sex" to "I have lost interest in sex completely")
PHY	General physical health	**SF** physical scale
IMP	Self-reported improvement	-
TIR	Feeling tired	**BDI -20** (Tiredness of fatigue, from "I am no more tired or fatigued than usual" to "I am too tired or fatigued to do most of the things I used to do"), **BDI -15** (Loss of energy, from "I have as much energy as ever" to "I don't have enough energy to do anything", **PHQ-4** ("Feeling tired or having little energy")
WOR	Feeling worried	**GAD-2** ("Not being able to stop or control worrying"), **GAD-3** ("Worrying too much about different things")
ANH	Loss of interest and pleasure in everyday life	**BDI-12** (Loss of interest, from "I have not lost interest in other people or activities" to "It's hard to get interested in anything"), **BDI-4** ("I get as much pleasure as I ever did from the things I enjoy" to "I can't get any pleasure from the things I used to enjoy"), **PHQ-1** ("Little interest or pleasure in doing things")
DIS	Disliking oneself	**BDI-14** (Worthlessness, from "I do not feel I am worthless" to "I feel utterly worthless"), **BDI-7** (Self-dislike, from "I feel the same about myself as ever" to "I dislike myself"), **BDI-8** (Self-criticalness, from "I don't criticise myself or blame myself more than usual" to "I blame myself for everything bad that happens"), **BDI-2** (Pessimism, from "I am not discouraged about my future" to "I feel my future is hopeless and will only get worse")
RES	Being restless or slow	**GAD-5** ("Being so restless that it is hard to sit still"), **GAD-6** ("Becoming easily annoyed or irritable"), **BDI-11** (Agitation, from "I am no more restless or wound up than usual" to "I am so restless or agitated that I have to keep moving or doing something"), **GAD-4** ("Trouble relaxing"), **PHQ-8** ("Moving or speaking so slowly that other people could have noticed, or the opposite, being so fidgety or restless that you have been moving around a lot more than usual"), **BDI-17** (Irritability, from "I am not more irritable than usual" to "I am irritable all the time")
SUI	Suicidal thoughts	**BDI-9** (Suicidal thoughts or wishes, from "I don't have any thoughts of killing myself" to "I would kill myself if I had the chance"), **PHQ-9** ("Thoughts that you would be better off dead or hurting yourself in some way")
SAD	Feeling sad or depressed	**BDI-1** (Sadness, from "I do not feel sad" to "I am so sad or unhappy that I can't stand it"), **PHQ-2** ("Feeling down, depressed, or hopeless")
APP	Lack of appetite or eating too much	**BDI-18** (Changes in appetite, from "U have not experienced any change in my appetite" to "I have no appetite at all" to "I crave food all the time"), **PHQ-5** ("Poor appetite or overeating")
CON	Concentration problems	**BDI-19** (Concentration difficulty, from "I can concentrate as well as ever" to "I find I can't concentrate on anything"), **PHQ-7** ("Trouble concentrating on things, such as reading the newspaper or watching television")
SLE	Sleep problems	**BDI-16** (Changes in sleeping patterns, from "I have not experienced any change in my sleeping" to "I wake up 1-2 hours early and can't get back to sleep" or "I sleep most of the day"), **PHQ-3** ("Trouble falling asleep or staying asleep, or sleeping too much")

Supplementary Table 3: Sample size at each time point, for each group (placebo and sertraline) for each individual symptom included in networks.

time	2wk	2wk	6wk	6wk	12wk	12wk
group	placebo	sertraline	placebo	sertraline	placebo	sertraline
BAD	292	279	285	267	265	264
ANX	292	277	285	266	264	264
AFR	292	277	285	266	264	264
FAI	292	278	285	266	264	264
GUI	292	277	285	266	264	264
PUN	292	278	285	266	264	264
CRY	292	278	285	266	264	264
IND	292	278	285	266	264	264
LIB	289	274	285	266	260	260
PHY	291	275	277	254	264	263
IMP	292	279	285	267	265	264
TIR	292	279	285	267	265	264
WOR	292	277	285	266	264	264
ANH	292	279	285	267	265	264
DIS	292	278	285	266	264	264
RES	292	279	285	267	265	264
SUI	292	279	285	267	265	264
SAD	292	279	285	267	265	264
APP	292	279	285	267	265	264
CON	292	279	285	267	265	264
SLE	292	279	285	267	265	264

Supplementary Table 4: Results of linear mixed models

Df = Degrees of freedom; CI_low: lower confidence interval value, CI_high: higher confidence interval value

Symptom	Effect	Fvalue	Df	Eta	CI_low	CI_high	P value	Adjusted p value (FDR)
AFR	Group	11.14	1, 1071.9	0.01	0.002	0.026	0.001	0.002
AFR	Group x Time	1.65	1, 1517.5	0.001	0	0.007	0.2	0.466
AFR	Time	23.91	1, 1517	0.016	0.006	0.03	0	0
ANH	Group	18.19	1, 1075.6	0.017	0.005	0.035	0	0
ANH	Group x Time	3.04	1, 1571.5	0.002	0	0.009	0.081	0.285
ANH	Time	51.2	1, 1571.3	0.032	0.017	0.05	0	0
ANX	Group	16.68	1, 1070.2	0.015	0.004	0.033	0	0
ANX	Group x Time	3.43	1, 1566.3	0.002	0	0.009	0.064	0.285
ANX	Time	47.75	1, 1566.1	0.03	0.015	0.048	0	0
APP	Group	0.33	1, 1066.4	0	0	0.006	0.565	0.565
APP	Group x Time	0.47	1, 1551.6	0	0	0.004	0.493	0.69
APP	Time	29.95	1, 1551.2	0.019	0.008	0.034	0	0
BAD	Group	19.76	1, 1065.3	0.018	0.006	0.037	0	0
BAD	Group x Time	1.9	1, 1536.4	0.001	0	0.007	0.169	0.443
BAD	Time	51.36	1, 1536	0.032	0.017	0.052	0	0
CON	Group	8.14	1, 1069.4	0.008	0.001	0.021	0.004	0.008
CON	Group x Time	1.12	1, 1579.2	0.001	0	0.006	0.29	0.553
CON	Time	51.08	1, 1578.9	0.031	0.017	0.05	0	0
CRY	Group	4.17	1, 1058.8	0.004	0	0.015	0.041	0.058
CRY	Group x Time	0.98	1, 1578.8	0.001	0	0.005	0.321	0.56
CRY	Time	29.22	1, 1578.7	0.018	0.007	0.033	0	0
DIS	Group	20.54	1, 1073.2	0.019	0.006	0.038	0	0
DIS	Group x Time	4.46	1, 1607	0.003	0	0.01	0.035	0.285
DIS	Time	72.53	1, 1606.8	0.043	0.026	0.064	0	0
FAI	Group	7.72	1, 1072.7	0.007	0.001	0.021	0.006	0.008
FAI	Group x Time	3.77	1, 1567.6	0.002	0	0.01	0.052	0.285
FAI	Time	53.37	1, 1567.3	0.033	0.018	0.052	0	0
GUI	Group	4.06	1, 1065.7	0.004	0	0.015	0.044	0.058
GUI	Group x Time	0.27	1, 1569.4	0	0	0.004	0.601	0.749
GUI	Time	27.69	1, 1569.1	0.017	0.007	0.032	0	0
IMP	Group	17.32	1, 1073.7	0.016	0.004	0.034	0	0
IMP	Group x Time	3.27	1, 1628.2	0.002	0	0.009	0.071	0.285
IMP	Time	21.37	1, 1628.2	0.013	0.004	0.026	0	0

IND	Group	13.38	1, 1071.5	0.012	0.003	0.029	0	0.001
IND	Group x Time	8.75	1, 1507.3	0.006	0.001	0.016	0.003	0.066
IND	Time	38.15	1, 1507	0.025	0.012	0.042	0	0
LIB	Group	11.13	1, 1059.7	0.01	0.002	0.026	0.001	0.002
LIB	Group x Time	0.15	1, 1491.7	0	0	0.003	0.7	0.774
LIB	Time	3.16	1, 1491.4	0.002	0	0.009	0.076	0.079
PHY	Group	1.97	1, 1054.3	0.002	0	0.011	0.161	0.178
PHY	Group x Time	0.03	1, 1520.1	0	0	0.002	0.859	0.902
PHY	Time	0.03	1, 1520.1	0	0	0.002	0.864	0.864
PUN	Group	3.56	1, 1049.5	0.003	0	0.014	0.06	0.074
PUN	Group x Time	0.15	1, 1435.4	0	0	0.004	0.696	0.774
PUN	Time	29.51	1, 1435	0.02	0.008	0.037	0	0
RES	Group	8.52	1, 1070.9	0.008	0.001	0.022	0.004	0.007
RES	Group x Time	0.27	1, 1587.9	0	0	0.004	0.606	0.749
RES	Time	48.77	1, 1587.7	0.03	0.016	0.048	0	0
SAD	Group	17.81	1, 1075.2	0.016	0.005	0.034	0	0
SAD	Group x Time	0.89	1, 1614	0.001	0	0.005	0.347	0.56
SAD	Time	46.13	1, 1613.8	0.028	0.014	0.045	0	0
SLE	Group	3.3	1, 1070.1	0.003	0	0.013	0.07	0.081
SLE	Group x Time	0.01	1, 1587.1	0	0	0.001	0.934	0.934
SLE	Time	32.23	1, 1586.9	0.02	0.009	0.036	0	0
SUI	Group	7.97	1, 1070.2	0.007	0.001	0.021	0.005	0.008
SUI	Group x Time	0.59	1, 1596.8	0	0	0.005	0.442	0.662
SUI	Time	3.97	1, 1596.6	0.002	0	0.01	0.047	0.051
TIR	Group	0.61	1, 1066.1	0.001	0	0.007	0.436	0.457
TIR	Group x Time	1.47	1, 1534.1	0.001	0	0.007	0.225	0.472
TIR	Time	59.99	1, 1533.6	0.038	0.021	0.058	0	0
WOR	Group	14.66	1, 1069.7	0.014	0.003	0.03	0	0
WOR	Group x Time	2.02	1, 1555.8	0.001	0	0.007	0.156	0.443
WOR	Time	64.9	1, 1555.4	0.04	0.023	0.061	0	0

Supplementary Table 5: Contemporaneous network at week 2.

Node 1	Node 2	Edge estimate
BAD	AFR	0.128
ANX	AFR	0.065
TREAT	FAI	0.039
BAD	FAI	0.123
AFR	GUI	0.073
FAI	GUI	0.151
BAD	PUN	0.097
ANX	PUN	0.075
FAI	PUN	0.094
GUI	PUN	0.105
GUI	CRY	0.027
TREAT	IND	0.065
FAI	IND	0.030
CRY	IND	0.090
TREAT	LIB	0.082
CRY	LIB	0.081
IND	LIB	0.054
TREAT	PHY	-0.028
LIB	PHY	-0.124
BAD	IMP	0.109
GUI	IMP	0.026
IND	IMP	-0.038
LIB	IMP	0.031
PHY	IMP	0.067
TREAT	TIR	0.077
BAD	TIR	0.028
FAI	TIR	0.095
CRY	TIR	0.060
IND	TIR	0.057
PHY	TIR	-0.122
IMP	TIR	0.044
BAD	WOR	0.065
ANX	WOR	0.374
AFR	WOR	0.198
IMP	WOR	0.062
BAD	ANH	0.047
ANX	ANH	-0.064
PUN	ANH	0.032
CRY	ANH	0.064
IND	ANH	0.097
LIB	ANH	0.086
IMP	ANH	0.125
TIR	ANH	0.097
WOR	ANH	0.080
TREAT	DIS	-0.044
BAD	DIS	0.138
FAI	DIS	0.126
GUI	DIS	0.049
PUN	DIS	0.123
CRY	DIS	0.104
IND	DIS	0.038
IMP	DIS	0.043
TIR	DIS	0.083
ANH	DIS	0.054
TREAT	RES	-0.053
ANX	RES	0.152
AFR	RES	0.067
PUN	RES	0.082
IND	RES	0.061

TIR	RES	0.093
WOR	RES	0.144
TREAT	SUI	-0.039
BAD	SUI	0.082
FAI	SUI	0.071
GUI	SUI	0.147
CRY	SUI	0.031
IMP	SUI	0.050
TIR	SUI	-0.035
WOR	SUI	0.078
ANH	SUI	0.031
DIS	SUI	0.065
TREAT	SAD	-0.092
BAD	SAD	0.138
ANX	SAD	0.092
GUI	SAD	0.046
IND	SAD	0.080
PHY	SAD	0.137
IMP	SAD	0.131
TIR	SAD	0.042
ANH	SAD	0.204
DIS	SAD	0.071
RES	SAD	0.038
SUI	SAD	0.138
TREAT	APP	0.089
ANX	APP	-0.096
AFR	APP	0.039
FAI	APP	-0.057
CRY	APP	-0.089
IND	APP	0.138
LIB	APP	0.060
PHY	APP	-0.035
IMP	APP	0.064
WOR	APP	0.059
DIS	APP	0.055
RES	APP	0.097
SUI	APP	-0.040
ANX	CON	0.051
AFR	CON	0.025
CRY	CON	0.046
IND	CON	0.105
LIB	CON	0.133
PHY	CON	-0.055
IMP	CON	0.056
TIR	CON	0.083
ANH	CON	0.049
RES	CON	0.212
SAD	CON	0.043
FAI	SLE	0.061
GUI	SLE	0.063
IND	SLE	0.046
LIB	SLE	0.043
TIR	SLE	0.188
ANH	SLE	0.111
DIS	SLE	0.054
RES	SLE	0.080
APP	SLE	0.128
CON	SLE	0.039

Supplementary Table 6: Contemporaneous network at week 6.

Node 1	Node 2	Edge estimate
TREAT	BAD	-0.087
TREAT	AFR	-0.041
ANX	AFR	0.201
BAD	FAI	0.083
AFR	FAI	0.030
BAD	GUI	0.174
FAI	GUI	0.061
BAD	PUN	0.124
AFR	PUN	0.058
FAI	PUN	0.135
GUI	PUN	0.112
PUN	CRY	0.039
GUI	IND	0.084
TREAT	LIB	0.235
FAI	LIB	-0.050
PUN	LIB	0.119
CRY	LIB	0.034
LIB	PHY	-0.066
TREAT	IMP	-0.036
BAD	IMP	0.043
PUN	IMP	-0.123
CRY	IMP	0.042
PHY	IMP	0.103
BAD	WOR	0.173
ANX	WOR	0.368
AFR	WOR	0.152
IND	WOR	0.101
IMP	WOR	0.053
BAD	ANH	0.080
AFR	ANH	0.031
IND	ANH	0.143
LIB	ANH	0.058
IMP	ANH	0.118
TIR	ANH	0.061
BAD	DIS	0.150
FAI	DIS	0.209
GUI	DIS	0.128
PUN	DIS	0.141
CRY	DIS	0.051
IND	DIS	0.067

IMP	DIS	0.059
TIR	DIS	0.076
ANH	DIS	0.118
TREAT	RES	-0.098
ANX	RES	0.078
AFR	RES	0.096
IND	RES	0.047
LIB	RES	0.108
IMP	RES	0.062
TIR	RES	0.061
WOR	RES	0.152
AFR	SUI	0.030
GUI	SUI	0.038
PUN	SUI	0.040
IND	SUI	0.022
IMP	SUI	0.139
TIR	SUI	0.064
DIS	SUI	0.071
RES	SUI	0.039
TREAT	SAD	-0.027
BAD	SAD	0.195
ANX	SAD	0.114
FAI	SAD	0.032
GUI	SAD	0.048
CRY	SAD	0.081
PHY	SAD	0.064
IMP	SAD	0.164
TIR	SAD	0.033
WOR	SAD	0.068
ANH	SAD	0.112
DIS	SAD	0.094
RES	SAD	0.050
SUI	SAD	0.111
CRY	APP	0.071
IND	APP	0.079
LIB	APP	0.082
PHY	APP	-0.052
TIR	APP	0.051
WOR	APP	0.053
RES	APP	0.141
TREAT	CON	-0.046
PUN	CON	0.081

IND	CON	0.147
IMP	CON	0.079
TIR	CON	0.244
ANH	CON	0.148
RES	CON	0.117
SAD	CON	0.084
APP	CON	0.045
TREAT	SLE	0.219
FAI	SLE	0.092
TIR	SLE	0.166
RES	SLE	0.074
SAD	SLE	0.039
APP	SLE	0.196
CON	SLE	0.077

Supplementary Table 7: Contemporaneous network at week 12.

Node 1	Node 2	Edge estimate
TREAT	ANX	-0.057
BAD	AFR	0.178
ANX	AFR	0.101
BAD	FAI	0.080
ANX	FAI	0.091
BAD	GUI	0.179
ANX	GUI	0.044
FAI	GUI	0.115
BAD	PUN	0.095
AFR	PUN	0.044
FAI	PUN	0.131
GUI	PUN	0.125
ANX	CRY	0.033
AFR	CRY	0.068
PUN	CRY	0.052
ANX	IND	0.070
AFR	IND	0.055
GUI	IND	0.137
PUN	IND	0.072
CRY	IND	0.191
TREAT	LIB	0.132
CRY	LIB	0.044
TREAT	PHY	-0.055
ANX	PHY	-0.058
PUN	PHY	0.043
ANX	IMP	0.064
AFR	TIR	0.047
CRY	TIR	0.061
LIB	TIR	0.136
PHY	TIR	-0.129
IMP	TIR	0.036
BAD	WOR	0.105
ANX	WOR	0.305
AFR	WOR	0.152
FAI	WOR	0.050
IMP	WOR	0.046
TREAT	ANH	-0.103
AFR	ANH	0.041
FAI	ANH	0.056
GUI	ANH	0.059

PUN	ANH	0.082
LIB	ANH	0.045
PHY	ANH	-0.037
IMP	ANH	0.097
TIR	ANH	0.131
TREAT	DIS	-0.061
BAD	DIS	0.159
ANX	DIS	-0.113
FAI	DIS	0.139
GUI	DIS	0.126
PUN	DIS	0.072
CRY	DIS	0.078
PHY	DIS	-0.084
WOR	DIS	0.074
ANH	DIS	0.119
ANX	RES	0.114
AFR	RES	0.070
CRY	RES	0.098
LIB	RES	0.052
IMP	RES	0.038
TIR	RES	0.074
WOR	RES	0.071
ANH	RES	0.113
DIS	RES	0.095
BAD	SUI	0.099
ANX	SUI	0.096
FAI	SUI	0.039
PUN	SUI	0.060
ANH	SUI	0.049
DIS	SUI	0.142
BAD	SAD	0.235
LIB	SAD	0.066
PHY	SAD	0.142
IMP	SAD	0.252
TIR	SAD	0.084
WOR	SAD	0.139
ANH	SAD	0.088
DIS	SAD	0.088
RES	SAD	0.091
SUI	SAD	0.121
TREAT	APP	0.099
BAD	APP	0.069

PUN	APP	0.032
CRY	APP	0.052
ANH	APP	0.103
IND	CON	0.181
TIR	CON	0.150
ANH	CON	0.102
RES	CON	0.233
SAD	CON	0.076
APP	CON	0.113
TREAT	SLE	0.065
ANX	SLE	0.068
TIR	SLE	0.227
ANH	SLE	0.040
RES	SLE	0.059
APP	SLE	0.122
CON	SLE	0.084

Supplementary Table 8: Temporally lagged network between 2 and 6 weeks.

Time 1 Node	Time 2 Node	Edge estimate
BAD	BAD	0.224
ANX	BAD	0.000
AFR	BAD	0.097
FAI	BAD	0.000
GUI	BAD	0.000
PUN	BAD	0.000
CRY	BAD	0.000
IND	BAD	0.000
LIB	BAD	0.000
PHY	BAD	0.000
IMP	BAD	0.000
TIR	BAD	0.000
WOR	BAD	0.000
ANH	BAD	0.000
DIS	BAD	0.000
RES	BAD	0.000
SUI	BAD	0.132
SAD	BAD	0.000
APP	BAD	0.000
CON	BAD	0.000
SLE	BAD	0.000
TREAT	BAD	-0.090
BAD	ANX	0.000
ANX	ANX	0.270
AFR	ANX	0.149
FAI	ANX	0.000
GUI	ANX	0.000
PUN	ANX	0.000
CRY	ANX	0.000
IND	ANX	0.000
LIB	ANX	0.000
PHY	ANX	0.000
IMP	ANX	0.000
TIR	ANX	0.000
WOR	ANX	0.000
ANH	ANX	0.000
DIS	ANX	0.000
RES	ANX	0.000
SUI	ANX	0.134
SAD	ANX	0.000

APP	ANX	0.000
CON	ANX	0.000
SLE	ANX	0.000
TREAT	ANX	-0.110
BAD	AFR	0.000
ANX	AFR	0.135
AFR	AFR	0.361
FAI	AFR	0.108
GUI	AFR	-0.178
PUN	AFR	0.000
CRY	AFR	0.000
IND	AFR	0.098
LIB	AFR	0.000
PHY	AFR	0.000
IMP	AFR	0.000
TIR	AFR	0.000
WOR	AFR	0.000
ANH	AFR	0.000
DIS	AFR	0.000
RES	AFR	0.000
SUI	AFR	0.087
SAD	AFR	0.000
APP	AFR	0.000
CON	AFR	-0.092
SLE	AFR	0.000
TREAT	AFR	-0.114
BAD	FAI	0.103
ANX	FAI	0.000
AFR	FAI	0.097
FAI	FAI	0.108
GUI	FAI	0.000
PUN	FAI	0.000
CRY	FAI	0.000
IND	FAI	0.000
LIB	FAI	-0.164
PHY	FAI	0.000
IMP	FAI	0.000
TIR	FAI	0.138
WOR	FAI	0.000
ANH	FAI	0.000
DIS	FAI	0.000
RES	FAI	0.000

SUI	FAI	0.098
SAD	FAI	0.000
APP	FAI	0.000
CON	FAI	0.000
SLE	FAI	0.000
TREAT	FAI	0.000

Supplementary Table 9: Temporally lagged network between 6 and 12 weeks.

Time 1 Node	Time 2 Node	Edge estimate
BAD	BAD	0.249
ANX	BAD	0.139
AFR	BAD	0.000
FAI	BAD	0.000
GUI	BAD	0.000
PUN	BAD	0.149
CRY	BAD	0.000
IND	BAD	0.100
LIB	BAD	0.000
PHY	BAD	-0.087
IMP	BAD	0.000
TIR	BAD	0.000
WOR	BAD	0.000
ANH	BAD	0.000
DIS	BAD	0.000
RES	BAD	0.000
SUI	BAD	0.112
SAD	BAD	0.000
APP	BAD	0.000
CON	BAD	0.000
SLE	BAD	0.000
TREAT	BAD	0.000
BAD	ANX	0.000
ANX	ANX	0.249
AFR	ANX	0.000
FAI	ANX	0.000
GUI	ANX	0.000
PUN	ANX	0.000
CRY	ANX	0.121
IND	ANX	0.129
LIB	ANX	0.000
PHY	ANX	0.000
IMP	ANX	0.000
TIR	ANX	0.000
WOR	ANX	0.000
ANH	ANX	0.000
DIS	ANX	0.000
RES	ANX	0.204
SUI	ANX	0.095
SAD	ANX	0.000

APP	ANX	0.000
CON	ANX	0.000
SLE	ANX	0.000
TREAT	ANX	-0.092
BAD	AFR	0.000
ANX	AFR	0.000
AFR	AFR	0.320
FAI	AFR	0.000
GUI	AFR	0.000
PUN	AFR	0.000
CRY	AFR	0.000
IND	AFR	0.111
LIB	AFR	0.000
PHY	AFR	0.000
IMP	AFR	0.000
TIR	AFR	0.000
WOR	AFR	0.000
ANH	AFR	0.000
DIS	AFR	0.000
RES	AFR	0.000
SUI	AFR	0.000
SAD	AFR	0.000
APP	AFR	0.000
CON	AFR	0.000
SLE	AFR	0.000
TREAT	AFR	0.000
BAD	FAI	0.000
ANX	FAI	0.000
AFR	FAI	0.105
FAI	FAI	0.351
GUI	FAI	0.000
PUN	FAI	0.151
CRY	FAI	0.000
IND	FAI	0.000
LIB	FAI	0.000
PHY	FAI	-0.083
IMP	FAI	0.000
TIR	FAI	0.000
WOR	FAI	0.000
ANH	FAI	0.000
DIS	FAI	0.000
RES	FAI	0.000

SUI	FAI	0.000
SAD	FAI	0.166
APP	FAI	0.000
CON	FAI	0.000

Supplementary Table 10: Comparison of network edges between sertraline and placebo groups in temporally lagged networks.

Model fit indices and Chi-square comparison for Model 1, where all edges were set to be equal between sertraline and placebo groups, and Model 2, where edges were freely estimated; Df: Degrees of Freedom; AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion.

	AIC	BIC	X^2	X^2 difference	Df	Df difference	p-value
Model 2 *Different edges across groups*	53120	63257	5494		1302		
Model 1 *Equal edges across groups*	52343	58678	6480	986	2184	882	0.008