Neuroscience and Biobehavioral Reviews 155 (2023) 105431

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Transdiagnostic biomarkers of mental illness across the lifespan: A systematic review examining the genetic and neural correlates of latent transdiagnostic dimensions of psychopathology in the general population

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ARTICLE INFO

Keywords:
General psychopathology
Internalizing
Externalizing
Genomic
Polygenic scores
Brain structure
Brain function
Developmental
Lifespan

ABSTRACT

This systematic review synthesizes evidence from research investigating the biological correlates of latent transdiagnostic dimensions of psychopathology (e.g., the p-factor, internalizing, externalizing) across the lifespan. Eligibility criteria captured genomic and neuroimaging studies investigating general and/or specific dimensions in general population samples across all age groups. MEDLINE, Embase, and PsycINFO were searched for relevant studies published up to March 2023 and 46 studies were selected for inclusion. The results revealed several biological correlates consistently associated with transdiagnostic dimensions of psychopathology, including polygenic scores for ADHD and neuroticism, global surface area and global gray matter volume. Shared and unique associations between symptom dimensions are highlighted, as are potential age-specific differences in biological associations. Findings are interpreted with reference to key methodological differences across studies. The included studies provide compelling evidence that the general dimension of psychopathology reflects common underlying genetic and neurobiological vulnerabilities that are shared across diverse manifestations of mental illness. Substantive interpretations of general psychopathology in the context of genetic and neurobiological evidence are discussed.

1. Introduction

Mental illness is a leading contributor to the global burden of disease (Anon, 2022). The most recent estimates indicate that mental illness affects approximately 970 million people worldwide, corresponding to a 48.1% increase in the prevalence of psychiatric disorders since 1990 (Anon, 2022). Effective strategies for the prevention, diagnosis, and treatment of psychopathology are needed to reduce the global burden of mental illness. Biological research plays a critical role in the development of these strategies by informing our understanding of the etiology, course, and consequences of psychopathology (Wilson and Olino, 2021; Glannon, 2022; Cuthbert, 2014). This research broadly aims to identify valid and reliable biological markers of mental illness, in order to facilitate the development of effective preventative interventions (e.g., identifying at-risk individuals) and treatment approaches (e.g., predicting illness course, informing decision-making, pharmacological interventions). Importantly, identifying the biological underpinnings of mental illness also helps to validate and distinguish between different psychiatric phenotypes, which is critical to improving diagnostic accuracy and disentangling the inherent heterogeneity of psychiatric expression (Michelini et al., 2021; Smoller et al., 2019a; Cuthbert and Insel, 2013).

1.1. The categorical model of psychopathology

Despite decades of research and significant advances in genetic and neuroimaging methods, little progress has been made in identifying

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https://doi.org/10.1016/j.neubiorev.2023.105431
Received 12 July 2023; Received in revised form 26 September 2023; Accepted 21 October 2023
Available online 26 October 2023

disorder-specific biomarkers with demonstrated clinical significance (Venkatasubramanian and Keshavan, 2016). A growing number of researchers argue that this lack of progress is driven by reliance on the categorical model of psychopathology (Cuthbert and Insel, 2013; Waszczuk et al., 2020; Latzman and DeYoung, 2020), endorsed by both the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2013) and the International Classification of Diseases (ICD) (World Health Organization, 2016). Briefly, the categorical model of psychopathology organizes psychiatric symptoms into a set of discrete diagnostic categories, distinct from other forms of psychopathology and from normal functioning. However, research has consistently demonstrated that liability towards disorder follows a continuum, ranging from normal functioning to more severe expressions of mental illness (Markon et al., 2011; Krueger et al., 2018; Kotov et al., 2017a). Psychiatric disorders also frequently co-occur within the same individual (i.e., comorbidity) (Kessler, 1994; Caspi et al., 2020) and show marked heterogeneity in symptom presentation and severity between individuals (Caspi et al., 2020; Feczko et al., 2019). Overall, this research suggests that the structure of psychopathology is poorly aligned with the discrete categorical boundaries imposed by traditional classification systems. For this reason, the categorical approach is now widely considered to provide a suboptimal framework through which to investigate the biological underpinnings of mental illness.

1.2. Latent Dimensional Models of Psychopathology

Latent dimensional models offer a data-driven alternative to measuring psychiatric phenotypes. These models identify patterns of covariation across a range of observed psychiatric symptoms, traits, and/or disorders and typically organize the structure of psychopathology hierarchically (Kotov et al., 2017a, 2021; Wright, 2023). Psychiatric symptoms and traits (e.g., depression, anxiety, substance use, aggressive behavior) are positioned at the lowest level of the hierarchy and grouped into higher-order dimensions based on their patterns of covariation with one another (e.g., internalizing, externalizing) (Kotov et al., 2021, 2017b). Briefly, the internalizing dimension typically captures more emotionally-focused indicators of psychopathology (e.g., anxiety, depression, specific phobia), whilst the externalizing dimension captures those that are more behaviourally-focused (e.g., aggression, impulsivity, substance use). Other prominent transdiagnostic phenotypes include the thought disorder dimension (which typically captures indicators of psychoticism e.g., hallucinations, delusions, disorganized thought) and the neurodevelopmental dimension (which typically captures indicators of neurodevelopmental disorders e.g., autism spectrum, developmental co-ordination disorder, and attention-deficit/hyperactivity disorder symptoms). Importantly, a superordinate general dimension of psychopathology (often referred to as the p-factor) is positioned at the top of this hierarchical structure (Kotov et al., 2021). This general dimension accounts for the frequent co-occurrence of mental health problems and is thought to reflect an underlying liability towards the full spectrum of psychopathology (Caspi et al., 2014; Caspi and Moffitt, 2018a).

The most prominent model to emerge from structural research is the Hierarchical Taxonomy of Psychopathology (HiTOP), a data-driven, hierarchically based classification system for mental illness (Kotov et al., 2017a, 2021). Within the HiTOP model, a general dimension of psychopathology (i.e., the p-factor) is positioned at the top of a hierarchical framework. This higher-order dimension is subdivided into increasingly specific lower-order spectra (e.g., internalizing, externalizing, thought disorder) and sub-spectra (e.g., internalizing can be subdivided into distress and fear dimensions). The general dimension of psychopathology (i.e., the p-factor) is defined by patterns of covariation among specific/lower-order dimensions (e.g., internalizing, externalizing), which are in turn defined by patterns of covariation among individual symptoms, signs, and maladaptive traits (Kotov et al., 2017a). The hierarchical and dimensional structure of psychopathology captured by the HiTOP model has been extensively validated, as outlined in several previous reviews (Kotov et al., 2021, 2017b, 2020; Krueger et al., 2021; Watson et al., 2022).

Factor analytic methods are the most commonly used approaches to studying the latent structure of psychopathology, predominately including correlated-factor, higher-order, and bi-factor models. These models offer several advantages over traditional diagnostic categories in examining the biological basis of mental illness: 1) they directly model the observed correlational and dimensional structure of psychiatric symptoms and thereby provide more valid and reliable phenotypes; 2) they offer greater precision and increased statistical power; and 3) they enable investigating biological correlates at varying levels of specificity and across the entire spectrum of psychiatric expression (Waszczuk et al., 2020; Latzman and DeYoung, 2020; Zald and Lahey, 2017). Recent decades have seen a proliferation of research investigating the latent dimensional structure and underlying biology of psychopathology. This research is facilitated by the collection of large-scale datasets, primarily involving general population samples. Prominent examples include the Adolescent Brain and Cognitive Development (ABCD) Study (Satterthwaite et al., 2016), the Philadelphia Neurodevelopmental Cohort (PNC) (Satterthwaite et al., 2016), and the UK Biobank (Sudlow et al., 2015). These studies involve extensive multidimensional data collection, often including detailed psychiatric assessments, as well as both neuroimaging and genomic measures. They also recruit significantly large sample sizes, providing the necessary statistical power for analyses of high-dimensional (e.g., genomic, neuroimaging) data and increasing the generalizability of research findings.

1.3. Genetic and neuroscientific biomarkers of mental illness

The expression of psychopathology arises from a complex set of interactions between different biological mechanisms (e.g., genomic, brain structural, brain functional) and between biological and environmental factors more broadly. As such, both genetic and neuroscientific research are fundamentally important to understanding of the biological basis of mental illness and provide promising and widely explored avenues for the identification of psychiatric biomarkers. In recent years, molecular genetic research has shifted its focus from candidate gene studies to genome-wide approaches in aiming to identify the genetic architecture underlying complex traits and disorders (Duncan et al., 2019). For example, genome-wide association studies (GWASs) compare the frequencies of a large number (typically 500k-1 M) of common variants across the genome (e.g., single-nucleotide polymorphisms or SNPs) between cases of a given phenotype (e.g., depressed patients) and controls (Corvin et al., 2010; Tam et al., 2019). Summary statistics from these studies can then be used to calculate polygenic scores (PGSs) in independent samples, providing a single quantitative metric of genetic risk for a particular trait or disorder based on the aggregate effects of genetic variants found to be associated with that phenotype through the relevant GWAS (Lewis and Vassos, 2022). These approaches capture polygenetic influences on psychiatric phenotypes (i.e., the contribution of multiple genetic variants to a given disorder) and have consistently demonstrated evidence of widespread pleiotropy across different forms of mental illness (Lewis and Vassos, 2022; Smoller et al., 2019b; Lee et al., 2021). That is, genetic variants influencing the expression of psychopathology are largely shared across putatively distinct diagnostic categories (Waszczuk et al., 2020).

Psychiatric neuroscience offers a complementary and interrelated approach to investigating the biological basis of mental illness. Generally, magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) are used to investigate whether alterations in macroscopic (e.g., gray matter) and microscopic (e.g., white matter) features of brain morphology (i.e., brain structure) contribute to the expression of psychopathology. Alternatively, functional MRI (fMRI) measures changes in blood oxygenation levels as a proxy for neural activity and allows for investigating the functional neural correlates of mental illness. Resting-

state fMRI measures spontaneous fluctuations in neural activity in the absence of external stimulation whilst task-based fMRI measures changes in blood oxygen level dependent (BOLD) responses to an experimental task. Similar to genomic research, neuroscientific studies historically aimed to identify disorder-specific associations within discrete brain regions and have more recently begun to examine how psychopathology relates to the interactions between them and to the overall structural and functional architecture of the brain. Importantly, alterations in brain structure and function have also been implicated across a range of psychiatric disorders and evidence from meta-analytic research suggests that these associations are primarily shared across different diagnostic categories (Goodkind et al., 2015; McTeague et al., 2017; Sha et al., 2019). These findings indicate that the biological mechanisms associated with mental illness are consistent with the observed correlational structure of psychopathology identified through phenotypic research. Both genomic and neuroimaging studies also indicate that the biological mechanisms underlying different manifestations of psychopathology are associated with subclinical expressions of mental illness in the general population, which is further consistent with the observed dimensionality of psychiatric phenotypes (Martin et al., 2018; Besteher et al., 2020).

Whilst several previous reviews have examined the correlates of transdiagnostic dimensional phenotypes, most have not followed a systematic approach (Waszczuk et al., 2020; Latzman and DeYoung, 2020; Kotov et al., 2017a, 2021; Perkins, 2020; Conway et al., 2019). Furthermore, those which focused specifically on genetic or neuroimaging research examined only a select number of studies (Waszczuk et al., 2020; Latzman and DeYoung, 2020; Perkins*** et al., 2020). Research investigating the biological correlates of transdiagnostic symptom dimensions is rapidly developing and as such, it is important to provide a comprehensive overview and synthesis of the current evidence. A single review has systematically explored risk and protective factors (including biological factors) associated with transdiagnostic symptom dimensions but the included studies were restricted to a narrow age range (i.e., 10–24 years old) (Lynch et al., 2021). Whilst this was an important first step, research has long demonstrated age- and developmentally-specific differences in the expression of mental illness that are driven by normative and non-normative changes in genetic, neurobiological, and environmental factors (Wilson and Olino, 2021). Research across the lifespan is therefore critical to accurately modelling the structure and underlying biology of mental illness (Lahey et al., 2017). The aforementioned advantages of latent symptom dimensions over traditional diagnostic categories suggests that they may provide new insights into the etiology of mental illness and the biological mechanisms and processes associated with changes in the expression of psychopathology across different age groups and developmental periods. Moreover, this research may guide biologically-informed preventative and early intervention efforts (e.g., by identifying biomarkers that predict the onset of psychopathology), as well as the development of effective treatment strategies (e.g., by identifying biomarkers associated with active psychopathology, or prolonged exposure to psychopathology, which provide targets for pharmacological intervention) (Beauchaine et al., 2008).

1.4. The present review

The present review aims to extend previous research by systematically evaluating evidence from studies investigating the biological correlates of latent transdiagnostic symptom dimensions in the general population, across the lifespan. The review covers a wide range of biological correlates (i.e., genomic, brain structural, and brain functional) at various levels of specificity (i.e., general and specific transdiagnostic symptom dimensions). Synthesizing this research will provide a comprehensive understanding of the current evidence base and identify promising and understudied directions for future research aiming to advance the field.

2. Methods

2.1. Study protocol

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Appendix A, Table S1). The study protocol was published prospectively (Hoy et al., 2022) and registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42021262717). Deviations from the protocol are outlined in Appendix A.

2.2. Search strategy

A comprehensive search strategy was employed across Embase, MEDLINE, and PsycINFO (Appendix B, Table S2). An initial search was run in July 2021 and re-run in March 2023. The search strategy captured three broad domains, including: latent variable models of psychopathology, genetics, and neuroimaging. Specifically, the overall strategy functioned as follows: (latent variable model terms AND psychopathology terms) AND (molecular genetic OR genomic terms) OR (brain structural OR brain functional neuroimaging terms). Reference lists of included articles were manually searched for additional citations.

2.3. Study eligibility

Eligibility criteria were developed using the Population Exposure Comparator Outcome (PECOS) framework. No criteria were imposed for the comparator component because research investigating dimensional models of psychopathology does not require the use of control groups (Lynch et al., 2021). The following inclusion and exclusion criteria were applied:

2.3.1. Inclusion criteria

Population.

Only studies investigating general population samples were eligible for inclusion.
Studies investigating any age group were eligible.
Only studies investigating human participants were eligible.

Exposure.

Studies using any latent variable modelling technique (e.g., factor analysis, principal component analysis, structural equation modelling) to investigate symptom- or disorder-level latent transdiagnostic dimensions as the exposure were eligible for inclusion.
- Studies investigating any latent transdiagnostic dimension(s) of psychopathology (e.g., general psychopathology, externalizing, internalizing, thought disorder) were eligible.
- Studies investigating any latent structural model(s) of psychopathology (e.g., bifactor models, hierarchical models, correlated factor models) were eligible.

Studies using any technique to investigate molecular genetic or genomic variables as the exposure (with the exception of candidate gene studies) were eligible for inclusion.
Studies using any neuroimaging technique to investigate any brain structural or brain functional variable as the exposure were eligible for inclusion.
Both whole-brain and region of interest neuroimaging studies were eligible.

Outcomes.

For studies that treat psychiatric phenotypes (i.e., symptom- or disorder-level latent transdiagnostic dimensions) as the exposure, the outcome measure must include at least one biological variable (i.

e., molecular genetic, genomic, brain structural, and/or brain functional).
For studies that treat biological variables as the exposure, at least one symptom- or disorder-level latent transdiagnostic dimension (e.g., general psychopathology, externalizing, internalizing) must be measured as the outcome.
Only studies reporting empirical data were included.

Study characteristics.

Only peer-reviewed studies were included.
Both cross-sectional and longitudinal studies were eligible. For longitudinal studies, all timepoints were considered.
Studies including any sample size were eligible.
Studies written in any language were eligible.

2.3.2. Exclusion criteria

Population.

With the exception of severe psychopathology (e.g., schizophrenia, autism), studies in which participants were included or excluded based on clinical symptoms, psychiatric disorders, or relevant risk factors (e.g., history of abuse, neglect, or maltreatment) were not eligible for inclusion.
Studies of non-human animals were excluded.

Exposures/Outcomes.

Studies investigating individual symptoms, signs, or maladaptive traits that are shared across diagnostic categories were excluded.
Studies in which psychopathology was not measured using latent variable techniques (e.g., total scores on transdiagnostic instruments) were excluded.
Studies that included biometric genetic measures (e.g., twin, family, and adoption studies) were excluded.
Candidate gene studies were excluded.
Neurophysiological studies (e.g., studies using electroencephalography to measure neural activity) were excluded.
Neuroscientific studies using techniques other than neuroimaging (e.g., post-mortem studies) were excluded.

Study characteristics.

Grey literature and conference abstracts were excluded.
Publications that did not report original empirical findings (e.g., reviews, opinion pieces, letters, books, or book chapters) were excluded.

2.4. Selection procedure

Two reviewers (i.e., NH and SL) were involved in screening and study selection procedures. Following de-duplication, reviewer one (NH) screened all titles and abstracts to identify eligible studies. Reviewer two (SL) independently screened a random selection of 25% of the titles and abstracts to ensure accuracy of study selection. Following title and abstract screening, the full-texts of all included articles were screened by both reviewers to further assess study eligibility. Cohen's kappa was calculated to measure inter-rater agreement (for title and abstract screening and full-text screening) between the two reviewers, with a high level of agreement defined as a Cohen's kappa of.80 or above (McHugh, 2012). Disagreements were resolved through consultation among the two reviewers. Where disagreements could not be resolved, a third member of the research team (i.e., LM, SR, or MW) was consulted to reach consensus.

2.5. Data Extraction

All citations were imported to Covidence (Veritas Health Innovation, 2023) for title, abstract and full-text screening. Study data were extracted by NH using a data extraction spreadsheet developed by the research team.

2.6. Data synthesis and quality assessment

The results of all included genomic and neuroscientific (i.e., brain structural, and brain functional) studies are reported separately. Sufficient data were not available for meta-analyses and as such, a narrative synthesis of the results from included studies was conducted. Following data extraction, the quality of each included study was assessed independently by NH using checklists from the Joanna Briggs Institute (Moola et al., 2020). Cross-sectional studies were evaluated using the Checklist for Analytical Cross-Sectional Studies and longitudinal studies were evaluated using the Checklist for Cohort Studies (Moola et al., 2020).

3. Results

3.1. Selection of studies

The search strategy returned 7010 studies (after de-duplication) across the three databases. Of these, 173 remained eligible for inclusion following title and abstract screening. After full-text screening and manual search of citations, 46 studies were selected for inclusion in the review. Cohen's kappa showed a moderate level of agreement for title and abstract screening ($k = 0.56$) and for full-text screening ($k = 0.48$). The PRISMA flow chart is provided in the supplementary material (Appendix A, Fig. S1). Quality assessments for each of the included studies are presented in Table S3 (Appendix B).

3.2. Characteristics of included studies

A broad overview of study characteristics is presented in Table 1. Briefly, the review included 18 genomic studies, 14 structural neuroimaging studies, 11 functional neuroimaging studies, one study that included both structural and functional neuroimaging measures, and two studies that included both genomic and brain structural measures. There were 16 unique datasets used across the included studies, most commonly from the ABCD Study ($n = 13$) and the PNC ($n = 9$; see Appendix B, Table S4). The majority of included studies investigated samples of youth (i.e., childhood to young adulthood). In the genomics literature, 13 out of the 18 studies included participants aged 7–22 years old. One study examined latent trajectories of externalizing between the ages of 18–32 and the remaining studies included wide age ranges, from adulthood to older adulthood (ages 18–64, 25–75) or midlife to older adulthood (ages 37–73, 40–69, 51–83). In the structural neuroimaging literature, 10 of the 14 studies examined participants aged 6–23 years old. Of the remaining studies, one examined latent disinhibition in the UK Biobank (ages 40–69) and three examined participants form the Dunedin Study (age 45) (age 45). The 11 included functional neuroimaging studies examined samples ranging from childhood to young adulthood (ages 9–23) and almost half used participants from the ABCD Study ($n = 5$). Not a single included study across any domain (i.e., genomic, neuroimaging) focused specifically on older adults (i.e., samples aged 60 +). In terms of study design, 32 of the included studies were cross-sectional and 14 were longitudinal. The following section synthesizes evidence for relationships between transdiagnostic symptom dimensions and biological variables that were investigated across two or more of the included studies, as well as any notable trends that emerged. Key findings from the genomics and structural neuroimaging literature are presented in Table 2 and Table 3, respectively. For detailed summaries of all included studies (including effect sizes, where available)

Table 1
Overview of studies included in the review.

Authors	Sample	Age	Design	Analytic Sample Size	Latent Dimensional Model (s)	Transdiagnostic symptom dimensions	Biological variable (s)
1. Genomic Studies							
Allegrini et al. (2020)	TEDS	7 (T1); 9 (T2); 12 (T3); 16 (T4)	L	N = 7026	PCA	General psychopathology	Genomic p-factor (derived from PGSs for ASD, MDD, BIP, SCZ, ADHD, OCD, AN, PTSD)
Avinun et al. (2020)	DNS	18–22	CS	N = 522	Bi-factor model	General psychopathology, internalizing, externalizing, thought disorder	PGSs for vitamin D serum levels
Birkell et al. (2020)	CATSS	9–12	CS	N = 13,457	(1) Bi-factor model (2) Bi-factor model	(1) General psychopathology (2) General psychopathology	PGSs for ADHD
Chen et al. (2022)	CATSS	9–12 (T1), 15 (T2)	L	N = 3907	(1) Bi-factor (S-1) model (2) Bi-factor (S-1) model	(1) General psychopathology (T1) (2) General psychopathology, emotional symptoms (i.e., internalizing) (T2)	PGSs for SCZ, BIP, MDD, neuroticism, ANX, PTSD, eating disorder, ASD, ADHD, ADHD symptoms, education, intelligence
Cuevas et al. (2021)	MIDUS Biomarker Project	25–75	CS	N = 1146	Two-factor model	Anxiety/negative affect (i.e., anxious-misery)	PGSs for ANX, MDD, and neuroticism
Gard et al. (2021)	HRS	51–83	CS	N = 3001	One-factor model	General psychopathology	General PGSs, internalizing-specific PGSs and externalizing-specific PGSs, as well as PGSs for MDD, ANX, ADHD, alcohol dependence, antisocial behaviour, cannabis, neuroticism, and height
Grotzinger et al. (2019)	UK Biobank	40–69	CS	N = 332,050	Bi-factor model	General psychopathology	General PGSs and PGSs for SCZ, BIP, MDD, ANX, PTSD
Jermy et al. (2022)	UK Biobank	37–73	CS	N = 119,692	Higher-order model	Internalizing	PGSs for MDD and height
Jones (2018)	ALSPAC	16	CS	N = 2863	(1) Bi-factor model (2) Correlated-factor model	(1) General psychopathology, psychotic experiences (i.e., thought disorder) (2) Psychotic experiences (i.e., thought disorder)	PGSs for SCZ, MDD, BIP, and neuroticism
Lahey et al. (2022)	ABCD	9–10 (T1), 10–11 (T2)	L	N = 4342	Bi-factor model	General psychopathology, internalizing	PGSs for ADHD
Li et al. (2019)	Add Health	18–26 (T1), 24–32 (T2)	L	N = 7674	LCG model	Normal (consistently low levels), high decreasing (high initial symptoms that decrease over time), moderate (consistently moderate levels), and low increasing (low initial symptoms that increase over time) trajectories of externalising.	PGSs for ADHD
Mollon et al. (2021)	PNC	8–22	CS	N = 4662	(1) Bi-factor model (2) Higher-order model	General psychopathology, anxious-misery, fear, externalizing, psychosis (i.e., thought disorder)	SNP-heritability; genetic correlations; and gene by age interactions
Neumann et al. (2016)	Generation R	6–8	L*	N = 2115	Bi-factor model	General psychopathology, internalizing, externalizing	SNP-heritability
Musci et al. (2016)	Community sample	11 (T1), 17 (T2)	L*	N = 488	LTSO model	Latent trait measure of internalizing	PGSs for MDD
Pat et al. (2022)	ABCD	9–10	CS	N = 4814	(1) Higher-order model (2) Correlated-factors model	(1) General psychopathology (2) Internalizing, externalizing, neurodevelopmental, somatic, detachment	PGSs for MDD, ADHD, ANX, BIP, SCZ, and ASD
Quattrone et al. (2021)	EU-GEI (population-based control group)	18–64	CS	N = 1497	Bi-factor model	General psychotic symptoms (i.e., thought disorder)	PGSs for SCZ
Riglin et al. (2020)	ALSPAC	7 (T1), 13 (T2)	L	N = 5518	Bi-factor model	General psychopathology, emotional (i.e., internalizing), behavioural (i.e., externalizing), neurodevelopmental	PGSs for SCZ, ADHD, ASD, MDD
Waszczuk et al. (2022)	ABCD	9–10	CS	N = 4717	(1) One-factor model (2) Five-factor model	(1) General psychopathology (2) Internalizing, externalizing, neurodevelopmental, somatoform, detachment	PGSs for adventurousness, disinhibition, number of sexual partners, risk tolerance, drinks per week (1), drinks per week (2), ever smoked regularly, depression, neuroticism, PTSD, insomnia, BIP, SCZ, ADHD, ASD, knee pain, chronic multisite pain, chronic back pain, educational

(*continued on next page*)

Table 1 (*continued*)

Authors	Sample	Age	Design	Analytic Sample Size	Latent Dimensional Model (s)	Transdiagnostic symptom dimensions	Biological variable (s)
							attainment, intelligence, Alzheimer's disease, BMI
2. Structural Neuroimaging Studies							
Cardenas-Iniguez et al. (2021)	ABCD	9–10	CS	N = 8588	Bi-factor model	General psychopathology, internalizing	FA and MD
Caspi et al. (2020)	Dunedin	45	L*	N = 875	(1) Bi-factor model (2) Correlated-factor model	(1) General psychopathology (2) Internalizing, externalizing, thought disorder	Brain age derived from multiple structural measures (i.e., cortical thickness, cortical surface area, subcortical volume)
Durham et al. (2021)	ABCD	9–10	CS	N = 9607	Bi-factor model	General psychopathology, internalizing	GMV
Kaczkurkin et al. (2019)	PNC	8–21	CS	N = 1394	Bi-factor model	General psychopathology, anxious-misery, psychosis (i.e., thought disorder), behavioural (i.e., externalizing), and fear	CT and GMV
Mewton et al. (2022)	ABCD	9–10	CS	N = 10,868	Higher-order model	General psychopathology, internalizing, externalizing, thought disorder	CT, SA, and cortical and subcortical GMV
Moberget et al. (2019)	PNC	8–23	CS	N = 1401	PCA	General psychopathology	CT, cerebellar GMV, subcortical GMV
Neumann et al. (2020)	Generation R	6–10	L*	N = 3030	Bi-factor model (with correlated specific factors orthogonal to the general factor)	General psychopathology, internalizing, externalizing	FA, MD, AD, RD; ROI-based analyses of FA in the left pons, two regions in the right pons, the left and right lemniscus, and the medial peduncle (i.e., attempted replication ofRomer et al., 2018)
Parkes et al. (2021)	PNC	8–22	CS	N = 1271	Bi-factor model	General psychopathology, anxious-misery, fear, externalizing, psychosis-positive, psychosis-negative	GMV measured as raw cortical volume and as deviations from normative cortical volume
Romer et al. (2018)	DNS	18–22	CS	MRI analysis: N = 1200 DTI analysis: N = 951	(1) Bi-factor model (2) Correlated-factor model	(1) General psychopathology (2) Internalizing, externalizing, thought disorder	GMV and FA
Romer et al. (2019)	Dunedin	45	L*	N = 875	Bi-factor model	General psychopathology	GMV and FA
Romer et al. (2021)	Dunedin	45	L*	N = 875	(1) Bi-factor model (2) Correlated-factor model	(1) General psychopathology (2) Internalizing, externalizing, thought disorder	CT, SA, GMV
Romer et al. (2023)	ABCD	9–10 (T1); 10–11 (T2); 11–12 (T3)	L	N = 9220	(1) Higher-order model (2) Bi-factor model	(1–2) General psychopathology, internalizing, externalizing, neurodevelopmental, somatic, and detachment	CT, SA, and cortical and subcortical GMV
Snyder et al. (2017)	Community sample	6–10	L*	N = 254	(1) Bi-factor model (2) Correlated-factor model	(1) General psychopathology, internalizing, externalizing (2) Internalizing, externalizing	GMV
van Rooij et al. (2021)	UK Biobank	40–69	CS	N = 15,258	PCA	Behavioural disinhibition	Independent components of GMV *Note.* characterised by high loadings in the temporal/parietal and frontal cortices (component 1), occipital and frontal cortices (component 2), temporal cortex and subcortical regions (component 3), and the temporal cortex (component 4).
3. Functional neuroimaging studies							
Cui et al. (2022)	PNC	8–23	CS	N = 790	(1) Correlated-factor model (2) Bi-factor model	(1) Fear, anxious-misery, externalizing, psychosis (2) General psychopathology, fear, anxious-misery, externalizing, psychosis (i.e., thought disorder)	Functional network topography
Elliot et al. (2018)	DNS	18–22	CS	N = 605	Bi-factor	General psychopathology	Connectome-wide intrinsic functional connectivity
Hong et al. (2023)	ABCD	9–10	CS	N = 6905	One-factor model	General psychopathology	Within- and between-network connectivity (AUD, CON, CPN, DMN, DAN, FPN, RST, SAL, SMM, SMH, VAN, VIS, and 'unassigned' network)
Kaczkurkin et al. (2018)	PNC	11–23	CS	N = 833	Bi-factor model	General psychopathology, anxious-misery, fear, behavioural (i.e., externalizing), psychosis (i.e., thought disorder)	Regional cerebral blood flow and seed-based functional connectivity of the dorsal anterior cingulate
Karcher et al. (2021)	ABCD	9–10	CS	Discovery: N = 3790	Nested hierarchical linear models	(1) General psychopathology (2) internalizing and externalizing	Within- and between-network connectivity (AUD, CON, CPN,

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Table 1 (*continued*)

Authors	Sample	Age	Design	Analytic Sample Size	Latent Dimensional Model (s)	Transdiagnostic symptom dimensions	Biological variable (s)
				Replication: N = 3791	derived from EFA (using oblique rotation): (1) One-factor model (2) Two-factor model (3) Three-factor model (4) Four-factor model (5) Five-factor model	(3) internalizing, externalizing, neurodevelopmental (4) internalizing, externalizing, neurodevelopmental. somatoform (5) internalizing, externalizing, neurodevelopmental, somatoform, detachment	DMN, DAN, FPN, RST, SAL, SMM, SMH, VAN, VIS, and an 'unassigned' network)
Kim-Spoon et al. (2021)	Community sample	13–14 (T1), 14–15 (T2), 15–16 (T3), 16–17 (T4)	L	N = 167	LCSM	Substance use	ROI-based analysis of task-based (i.e., economic lottery choice task) neural activation in the insula cortex
Lees et al. (2021)	ABCD	9–10	CS	N = 9074	Higher-order model	General psychopathology, internalizing, externalizing, thought disorder	Within- and between-network functional connectivity (CON, CPN, DMN, DAN, FPN, RST, SAL, VAN, AUD, SMH, SMM, VIS) and connectivity between these networks and several subcortical ROIs (cerebellum, thalamus, caudate, putamen, pallidum, hippocampus, amygdala, nucleus accumbens, ventral diencephalon) Task-based (i.e., emotional n-back task) neural activation across large-scale functional networks
Shanmugan et al. (2016)	PNC	8–22	CS	N = 1129	Bi-factor model	General psychopathology, anxious-misery, fear, behavioural (i.e., externalizing), psychosis (i.e., thought disorder)	Task-based (i.e., fractal n-back task) neural activation across large-scale functional networks
Sripada et al. (2021)	ABCD	9–10	CS	N = 6593	Bi-factor	General psychopathology	Within- and between-network functional connectivity (DMN, VIS, FPN, SAL, VAN, DAN, CPN, RST, AUD, CON, SMM, SMH, the cerebellum, a subcortical network, and an 'unassigned' network)
Xia et al. (2018)	PNC	8–22	CS	Discovery: N = 663 Replication: N = 336	sCCA	Mood (i.e., anxious-misery), psychosis (i.e., thought disorder), fear, externalizing	Whole-brain resting state functional connectivity
Zhang et al. (2022)	UK Biobank	40–69	CS	N = 6389	CCA	General psychopathology	Amplitude and connectivity strength in the DMN, SAL, and CEN
3. Structural and functional neuroimaging studies							
Modabbernia et al. (2022)	ABCD	9–10	CS	MRI analysis: N = 8114 DTI analysis: N = 7171 fMRI analysis: N = 5484	(1) ICA (2) EFA (3) ICA (4) EFA	(1) Negative affect (i.e., internalizing), opposition-disinhibition (i.e., externalizing), cognitive dyscontrol (i.e., neurodevelopmental) (2) Internalizing, externalizing, neurodevelopmental (3) Negative affect (i.e., internalizing), opposition-disinhibition (i.e., externalizing), cognitive dyscontrol (i.e., neurodevelopmental), somatic (4) Internalizing, externalizing, neurodevelopmental, somatic, detachment	CT, SA, GMV, FA, MD, RD, AD, within- and between-network functional connectivity
4. Genomic and structural neuroimaging studies							
Alnaes et al. (2018)	PNC	8–22	CS	Genomic analysis: N = 2946	ICA	General psychopathology	SNP-heritability; multimodal DTI measures of white matter microstructural and connectivity features (i.e., fractional

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Table 1 (*continued*)

Authors	Sample	Age	Design	Analytic Sample Size	Latent Dimensional Model (s)	Transdiagnostic symptom dimensions	Biological variable (s)
				DTI analysis: N = 748			anisotropy, the principal DTI eigen value, radial diffusivity, mean diffusivity, mode of anisotropy, dominant fiber population, secondary fiber population, and connectivity density) decomposed into independent components (using ICA)
Fernandez-Cabello et al. (2022)	ABCD	9–10	CS	N = 7124	CCA	Internalizing and externalizing	General PGSs (derived from PGSs for AN, ADHD, ASD, BIP, MDD, OCD, SCZ, and Tourette syndrome) and PGSs for ADHD, ASD, BIP, MDD, OCD, SCZ, educational attainment; Several brain structural measures (i.e., CT, SA, WMV, FA and several measures of diffusivity)

Note. The table above provides a broad overview of studies included in the review. Symptom dimensions that were measured within a given latent variable model but were not treated as transdiagnostic dimensions are not reported (for full description of structural models see Appendix B, Tables S5-7). ABCD: Adolescent Brain and Cognitive Development Study; AD: axial diffusivity; Add Health: The National Longitudinal Study of Adolescent to Adult Health; ADHD: attention-deficit/hyperactivity disorder; ALSPAC: Avon Longitudinal Study of Parents and Children; AN: anorexia nervosa; ANX: anxiety; ASD: autism spectrum disorder; AUD: auditory network; BIP: bipolar disorder; CATSS: Child and Adolescent Twins Study in Sweden; CS: cross-sectional; CT: cortical thickness; CON: cingulo-opercular network; CPN: cingulo-parietal network; CCA: canonical correlation analysis; CEN: central executive network; DAN: dorsal attention network; DMN: default mode network; DNS: Duke Neurogenetics Study; DTI: diffusion tensor imaging; EFA: exploratory factor analysis; EU-GEI: European Network of National Schizophrenia Networks Studying Gene-Environment Interactions; FA: fractional anisotropy; FPN: frontoparietal network; fMRI: functional magnetic resonance imaging; GMV: gray matter volume; HRS: Health and Retirement Study; ICA: independent component analysis; L: longitudinal; LCSM: latent change score model; LGC: latent growth curve model; LTSO: latent state-trait-occasion model; MD: mean diffusivity; MDD: major depressive disorder; MIDUS: Midlife in the United States Study; MRI: magnetic resonance imaging; OCD: obsessive-compulsive disorder; PCA: principal component analysis; PGS: polygenic scores; PNC: Philadelphia Neurodevelopmental Cohort; PTSD: posttraumatic stress disorder; RD: radial diffusivity; ROI: region of interest; RST: retrosplenial-temporal network; SA: surface area; SAL: Salience Network; sCCA: sparse canonical correlation analysis; SCZ: schizophrenia; SMH: sensorimotor- hand network; SMM: sensorimotor-mouth network; SNP: single nucleotide polymorphism; T1-4: Time 1–4; TEDS: Twins Early Development Study; VAN: ventral attention network; VIS: visual network; WMV: white matter volume.

see Appendix B (Tables S5-7).

3.3. Genomic studies

3.3.1. Polygenic risk scores

General PGSs.

General Psychopathology.

A polygenic p-factor (i.e., defined as the first principal component extracted from PGSs for a range of psychiatric disorders) was positively associated with general psychopathology across childhood and early adolescence (ages 7–16) (Allegrini et al., 2020) and in two studies spanning midlife to older adulthood (ages 40–83) (Grotzinger et al., 2019; Gard et al., 2021).

ADHD-PGSs.

General Psychopathology.

ADHD-PGSs were associated with greater general psychopathology across six studies, spanning childhood to adolescence (ages 7–16) (Riglin et al., 2020; Waszczuk et al., 2021; Pat et al., 2022; Lahey et al., 2022; Brikell et al., 2020; Chen et al., 2022) but showed no association with general psychopathology in one study of midlife and older adult participants (ages 51–83) (Gard et al., 2021).

Specific Transdiagnostic Symptom Dimensions.

Internalizing. The internalizing dimension was negatively associated with ADHD-PGSs in children (age seven) (Riglin et al., 2020) and showed mixed results in preadolescents and adolescents. ADHD-PGSs were negatively associated with internalizing in two studies of pre-adolescents (ages 9–10) from the ABCD study (at baseline but not at first follow-up) after controlling for general (Waszczuk et al., 2021; Lahey et al., 2022) and specific symptom dimensions (Lahey et al., 2022). However, another study of ABCD participants found no evidence of association with ADHD-PGSs when controlling for other PGSs (Pat et al., 2022). Two studies found no association between internalizing and disorder-level ADHD-PGSs in adolescents (ages 13, 15) (Riglin et al., 2020; Chen et al., 2022) but a significant negative association was observed between internalizing and symptom-level ADHD-PGSs at age 15 (Chen et al., 2022).

Externalizing. ADHD-PGSs showed no association with externalizing in bivariate analyses of preadolescents (ages 9–10) (Waszczuk et al., 2021); however, there was evidence of a positive association in analyses of the same sample when controlling for general and specific symptom dimensions, as well as multiple PGSs (Pat et al., 2022). ADHD-PGSs were also associated with 'high decreasing' and 'moderate' (but not low increasing) trajectories of externalizing between the ages of 18 and 32 based on longitudinal analyses using latent growth curve models (Li, 2019).

Neurodevelopmental. The neurodevelopmental dimension was not associated with ADHD-PGSs in childhood (age 7) (Riglin et al., 2020) but was positively associated with ADHD-PGSs in two studies of pre-adolescents (ages 9–10) (Waszczuk et al., 2021; Pat et al., 2022) from the ABCD study and in one study of adolescents (age 13) (Riglin et al., 2020).

Depression-PGSs.

General Psychopathology.

Two studies found a positive association between depression-PGSs and general psychopathology at baseline in the ABCD cohort (using one-factor and higher-order models) (Waszczuk et al., 2021; Pat et al., 2022). Another study found no association in a different sample of preadolescents (ages 9–12) when general psychopathology was modelled using a bi-factor approach (Chen et al., 2022). Depression-PGSs were also not associated with general psychopathology in childhood (age 7) (Riglin et al., 2020) or across three studies of adolescents (ages 13–16) (Riglin et al., 2020; Chen et al., 2022; Jones et al., 2018). However, they were positively associated with general psychopathology across two studies in midlife and older adulthood (Grotzinger et al., 2019; Gard et al., 2021).

Specific Transdiagnostic Symptom Dimensions.

Table 2
Associations between transdiagnostic symptom dimensions and polygenic scores investigated in two or more studies.

Authors	Age	Structural model (a)	G-PGS	ADHD					SCZ					DEP				NEUR		ASD				BIP	ANX	PTSD	INTEL		EDU	
			GP	GP	INT	EXT	ND	GP	INT	EXT	TD	ND	GP	INT	EXT	ND	GP	INT	GP	INT	EXT	ND	GP	GP	GP	GP	INT	GP	INT
Allegrini et al. (2020)	7	PCA																												
	9																													
	12																													
	16																													
Riglin et al. (2020)[1,2,3]	7	B-F																												
	13																													
Waszczuk et al. (2022)[1]	9-10	1-F, 5-F																												
Pat et al. (2022)[3]	9-10	H-O																												
Lahey et al. (2022)[1,2]	9-10	B-F																												
	10-11																													
Chen et al. (2022)[1,2,3]	9-12	B-F (S-1)																												
	15																													
Birkell et al. (2020)[1,2]	9-12	B-F																												
Jones (2018)[1,2]	16	B-F																												
Musci et al. (2016)	11-17	LTSO																												
Li et al. (2019)	18-32	LCG																												
Quattrone et al. (2021)	18-64	B-F																												
Cuevas et al. (2021)[3]	25-75	CF																												
Jermy et al. (2022)	37-73	H-O																												
Grotzinger et al. (2019)	40-69	B-F																												
Gard et al. (2021)	51-83	1-F																												

Note. This table details evidence of associations between polygenic scores and general/specific transdiagnostic symptom dimensions investigated in two or more included studies. Significant positive associations are highlighted in green, significant negative associations in blue, and non-significant associations in grey. Blank cells indicate that no association was tested. Cuevas et al. (2021) examined a latent anxiety/negative affect dimension (i.e., the anxious-misery subdimension of internalizing). 1-F: one-factor model; 5-F: five-factor model; ADHD: attention-deficit/hyperactivity disorder; ANX: anxiety; ASD: autism spectrum disorder; B-F: bi-factor model; BIP: bipolar; CF: confirmatory factor model; DEP: depression; EDUC: education; EXT: externalizing; GP: general psychopathology; G-PGS: general polygenic scores; H-O: higher-order model; INT: internalizing; INTEL: intelligence; LCG: latent growth curve model;; LTSO: latent trait-state-occasion model; ND: neurodevelopmental; NEUR: neuroticism; PCA: principal component analysis; PGS: polygenic scores; PTSD: posttraumatic stress disorder; SCZ: schizophrenia; TD: thought disorder.
[1]Study controlled for general psychopathology.
[2]Study controlled for other specific symptom dimensions.
[3]Study controlled for other PGSs.

Internalizing. Depression-PGSs showed no association with Internalizing in childhood (age 7), when modelled using a bi-factor approach and simultaneously regressing multiple PGSs (Riglin et al., 2020). Depression-PGSs were not associated with Internalizing in bivariate analyses of the ABCD cohort (after controlling for general psychopathology) (Waszczuk et al., 2021) but were positively associated in analyses controlling for general and specific symptom factors, as well as other PGSs (Pat et al., 2022). In a multivariate analysis of adolescents (age 13), Internalizing was positively associated with depression-PGSs but showed no association with five other polygenic exposures (Riglin et al., 2020). However, another study of adolescents at age 15 (controlling for general and specific symptom dimensions and other PGSS) found no evidence of association (Chen et al., 2022). Depression-PGSs also showed a positive association with a measure of Internalizing extracted from longitudinal assessment data across ages 11–17 (Musci et al., 2016). Depression-PGSs were not associated with a latent 'anxiety/negative affect' factor in a cross-sectional study of participants aged 25–75 (Cuevas et al., 2021) but were associated with a transdiagnostic measure of depressive and anxious symptoms in midlife to older adult participants from the UK Biobank (Jermy et al., 2022).

Table 3
Associations between transdiagnostic symptom dimensions and global/whole-brain measures of brain structure.

Authors	Age	Structural Model(s)	Neuroimaging: exposure/outcome	Brain Structural Associations								
				Cortical Thickness								
				GP	**INT**	**EXT**	**TD**	**ND**	**SOM**	**DET**	**A-M**	**FEAR**
Mewton et al. (2022)	9-10	H-O	Outcome	x	x	x	x					
Modabbernia et al. (2022)	9-10	ICA; EFA	Exposure									
Romer et al. (2023)	9-10 (T1)	H-O; B-F	Exposure									
	10-11 (T2)											
	11-12 (T3)											
Kaczkurkin et al. (2019)	8-21	B-F	Outcome	-		x	-					
Moberget et al. (2019)	8-23	PCA; ICA	Exposure	-			-					
Romer et al. (2021)	45	B-F; CF	Outcome	--	--	--	--					
				Surface Area								
				GP	**INT**	**EXT**	**TD**	**ND**	**SOM**	**DET**	**A-M**	**FEAR**
Mewton et al. (2022)[1]	9-10	H-O	Outcome	--	--	--	--					
Modabbernia et al. (2022)	9-10	ICA; EFA	Exposure									
Romer et al. (2023)[1]	9-10 (T1)	H-O; B-F	Exposure									
	10-11 (T2)			--								
	11-12 (T3)											
Romer et al. (2021)	45	B-F; CF	Outcome	x	x	x	x					
				Gray Matter Volume								
				GP	**INT**	**EXT**	**TD**	**ND**	**SOM**	**DET**	**A-M**	**FEAR**
Snyder et al. (2017)	6-10	B-F; C-F	Outcome	--	+	-						
Mewton et al. (2022)[1]	9-10	H-O	Outcome	--	--	--	--					
Durnham et al (2021)[1]	9-10	B-F	Outcome	--	x							
Modabbernia et al. (2022)	9-10	ICA; EFA	Exposure									
Romer et al. (2023)[1]	9-10 (T1)	H-O; B-F	Exposure									
	10-11 (T2)			--								
	11-12 (T3)											
Parkes et al. (2021)	8-22	B-F	Exposure	--		-	-				+	-
Kaczkurkin et al. (2019)[1]	8-22	B-F	Outcome	--		-	x				++	-
Romer et al. (2018)[1]	18-22	B-F; CF	Outcome	-								
Romer et al. (2021)[1]	45	B-F; CF	Outcome	-	-	-	-					

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Table 3 (*continued*)

Authors	Age	Structural Model(s)	Neuroimaging: exposure/outcome	Brain Structural Associations								
				Fractional Anisotropy								
				GP	INT	EXT	TD	ND	SOM	DET	A-M	FEAR
Neumann et al. (2020)[1]	6-10	B-F	Exposure	-	x	+						
Cardenas-Iniguez et al. (2021)	9-10	B-F	Exposure	x	x	x						
Modabbernia et al. (2022)	9-10	ICA; EFA	Exposure									
Romer et al. (2018)[1]	18-22	B-F; CF	Outcome	-								
				Mean Diffusivity								
				GP	INT	EXT	TD	ND	SOM	DET	A-M	FEAR
Neumann et al. (2020)	6-10	B-F	Exposure									
Cardenas-Iniguez et al. (2021)	9-10	B-F	Exposure	x	x							
Modabbernia et al. (2022)	9-10	ICA; EFA	Exposure									
				Radial Diffusivity								
				GP	INT	EXT	TD	ND	SOM	DET	A-M	FEAR
Neumann et al. (2020)	6-10	B-F	Exposure									
Modabbernia et al. (2022)	9-10	ICA; EFA	Exposure									
				Axial Diffusivity								
				GP	INT	EXT	TD	ND	SOM	DET	A-M	FEAR
Neumann et al. (2020)	6-10	B-F	Exposure									
Modabbernia et al. (2022)	9-10	ICA; EFA	Exposure									

Note. The table above provides a broad overview of evidence from two or more studies investigating the relationship between general and/or specific transdiagnostic symptom dimensions with global/whole-brain measures of brain structure. Coloured cells indicate whether associations with global brain structure were positive, negative, or non-significant (green, blue, and grey squares, respectively). For whole-brain analyses of regional associations, significant positive effects are indicated by a plus sign (+), significant negative effects by a minus sign (-), and analyses that found no evidence of significant associations are marked with an 'x'. One sign (e.g., +/-) indicates few regional associations and two signs (e.g., ++/–) indicates that associations were widespread. Blank cells indicate that no association was tested. Importantly, relationships between symptom dimensions and brain structure were counted as having been examined in more than one study regardless of differences in the construction of psychiatric phenotypes (e.g., psychiatric indicators, latent variable models), measurement of brain structure (e.g., global/whole-brain measures), or the direction of association investigated (e.g., whether neuroimaging variables were included as the exposure or outcome) across studies. In addition, some studies included analyses across multiple latent variable approaches and significant associations indicated here may refer only to one approach or both. A-M: anxious-misery; B-F: bi-factor model; CF: correlated-factors model; DET: detachment; EFA: exploratory factor analysis; EXT: externalizing; GP: general psychopathology; H-O: higher-order model; ICA: independent component analysis; INT: internalizing; ND: neurodevelopmental; PCA: principal component analysis; SOM: somatic; T1-2: time 1–2; TD: thought disorder.
[1]Study controlled for global effects (e.g., total GMV, total FA).

Neurodevelopmental. Depression-PGSs were not associated with the neurodevelopmental dimension in one study of the ABCD cohort (i.e., bivariate analyses controlling for general psychopathology) (Waszczuk et al., 2021) but were positively associated in another (i.e., multivariate analyses controlling for general and specific symptom dimensions as well as other PGSs) (Pat et al., 2022). One additional study found no evidence of an association between depression-PGSs and a neurodevelopmental dimension in childhood or adolescence (using a bi-factor model and controlling for other PGSs) (Riglin et al., 2020).

Externalizing, Somatic, and Detachment. In bivariate analyses (controlling for general psychopathology), there was no evidence of an association between depression-PGSs and externalizing, somatic, or detachment dimensions in preadolescents from the ABCD study. However, in multivariate analyses of the same sample, controlling for general and specific symptom factors, as well as other PGSs, all three symptom dimensions were positively associated with PGSs for depression (Pat et al., 2022).

Schizophrenia-PGSs.

General Psychopathology.

Schizophrenia-PGSs were associated with greater general psychopathology in childhood (age 7) (Pat et al., 2022) but showed no association across three studies of preadolescents (ages 9–12) (Waszczuk et al., 2021; Pat et al., 2022; Chen et al., 2022). Results were mixed for adolescents, with schizophrenia-PGSs associated with greater general psychopathology in two studies (ages 13–16) (Riglin et al., 2020; Jones et al., 2018) and showing no association in another (age 15) (Chen et al., 2022). General psychopathology was also positively associated with PGSs for schizophrenia in one study of midlife and older adults (ages 40–69) (Grotzinger et al., 2019).

Specific Transdiagnostic Symptom Factors.

Internalizing. Schizophrenia-PGSs were positively associated with Internalizing in children (Riglin et al., 2020) but showed no association across three studies spanning preadolescence (Waszczuk et al., 2021) and adolescence (Riglin et al., 2020; Chen et al., 2022).

Thought Disorder. PGSs for schizophrenia were positively associated with a positive psychosis dimension (when derived from a correlated-factors model but not a bi-factor model) and with a negative psychosis dimension (when derived from both a bi-factor and correlated-factors

model) adolescents (age 16) (Jones et al., 2018). In addition, schizophrenia-PGSs were positively associated with positive, negative, and general psychotic dimensions in participants aged 18–64 (Quattrone et al., 2021).

Neurodevelopmental. There was no evidence of an association with schizophrenia-PGSs and a neurodevelopmental dimension across two studies, spanning childhood and adolescence (ages 7–13) (Riglin et al., 2020; Waszczuk et al., 2021).

Autism-PGSs.

General Psychopathology.

One study found a positive association between general psychopathology and autism-PGSs based on bivariate analyses in preadolescents from the ABCD study (Waszczuk et al., 2021). However, three other studies found no evidence of an association across childhood and adolescence (ages 7–15), including in ABCD participants, when simultaneously controlling for other PGSs and/or specific symptom factors (Riglin et al., 2020; Pat et al., 2022; Chen et al., 2022).

Specific Transdiagnostic Factors.

Internalizing. Autism-PGSs were not associated with Internalizing across three studies, spanning childhood and adolescence (ages 7–15), (Riglin et al., 2020; Waszczuk et al., 2021; Chen et al., 2022).

Neurodevelopmental. Autism-PGSs were not associated with the neurodevelopmental dimension in childhood or adolescence (ages 7, 13) (Riglin et al., 2020) or in preadolescents from the ABCD study (after controlling for general psychopathology) (Waszczuk et al., 2021).

Bipolar-PGSs.

General Psychopathology.

Bipolar-PGSs were not associated with general psychopathology across four studies spanning preadolescence and adolescence (ages 9–15) (Waszczuk et al., 2021; Pat et al., 2022; Chen et al., 2022; Jones et al., 2018) but were positively associated in one study of midlife and older adulthood (40−69) (Grotzinger et al., 2019).

Specific Transdiagnostic Symptom Dimensions.

Internalizing. Bipolar-PGSs were not associated Internalizing across two studies, in preadolescents (ages 9–10) and adolescents (age 15) (Waszczuk et al., 2021; Chen et al., 2022).

Other. Bipolar-PGSs were also not associated with any symptom dimension that was investigated in a single study (i.e., externalizing, psychosis positive, psychosis negative, neurodevelopmental, somatic, and detachment), spanning preadolescence and adolescence (ages 9–10 and 16) (Waszczuk et al., 2021; Jones et al., 2018).

Neuroticism-PGSs.

General psychopathology.

Neuroticism-PGSs were positively associated with general psychopathology in bivariate analyses of preadolescents from the ABCD study (Waszczuk et al., 2021) but showed no association in another preadolescent sample that controlled for specific symptom factors and multiple PGSs (Chen et al., 2022). Neuroticism-PGSs were also positively associated with general psychopathology across two adolescent samples (ages 15–16) (Chen et al., 2022; Jones et al., 2018) and in a single study of midlife and older adulthood (ages 51–83) (Gard et al., 2021).

Specific Transdiagnostic Symptom Dimensions.

Internalizing. Neuroticism-PGSs were not associated with Internalizing (after controlling for general psychopathology) in preadolescents (ages 9–10) (Waszczuk et al., 2021) but were positively associated in adolescents (age 15) when controlling for other PGSs and latent factors (Chen et al., 2022). In addition, neuroticism-PGSs were positively associated with a 'anxiety/negative affect factor' in a cross-sectional study of participants aged 25–75 years old (Cuevas et al., 2021).

PTSD-PGSs.

General Psychopathology.

PGSs for PTSD were positively associated with general psychopathology in one study of ABCD participants (i.e., bivariate analyses controlling for general psychopathology) (Waszczuk et al., 2021) but not in another longitudinal study of preadolescents (ages 9 and 12) and adolescents (age 15) (controlling for general and specific symptom factors, as well as other PGSs) (Chen et al., 2022). General psychopathology was positively associated with PGSs for PTSD in one study of midlife and older adults (ages 51–83) (Gard et al., 2021).

Specific Transdiagnostic Symptom Dimensions.

Internalizing. PTSD-PGSs were not associated with Internalizing in preadolescents (after controlling for general psychopathology) (Waszczuk et al., 2021) or in a sample of adolescents (age 15) (Chen et al., 2022).

Anxiety-PGSs.

General Psychopathology.

Anxiety-PGSs showed no association with general psychopathology across two studies spanning childhood and adolescence (ages 9–15) (Pat et al., 2022; Chen et al., 2022) but were positively associated in two studies of midlife and older adult participants (ages 40–83) (Grotzinger et al., 2019; Gard et al., 2021).

Specific Transdiagnostic Symptom Dimensions.

Internalizing. PGSs for anxiety were not associated with Internalizing at age 15 (Chen et al., 2022) or with a 'anxiety/negative affect' factor in a cross-sectional study of participants aged 25–75 (Cuevas et al., 2021).

3.3.2. SNP-heritability

General Psychopathology.

Significant SNP-heritability was observed for general psychopathology in children (ages 6–8) from the Generation R cohort (Neumann et al., 2016). In youths from the PNC (ages 8–22), two studies found significant SNP heritability associated with general psychopathology; (Mollon et al., 2021; Alnæs et al., 2018) however, this association did not survive false discovery rate (FDR) correction in one study (Mollon et al., 2021).

3.4. Structural neuroimaging studies

3.4.1. Gray matter

Cortical thickness.

General Psychopathology.

Two studies found no evidence of an association between global cortical thickness and general psychopathology, either at baseline or across the first three waves of data collection, in preadolescents from ABCD study (ages 9–12) (Mewton et al., 2022a; Romer et al., 2023). In the PNC (ages 8–22), reduced cortical thickness was associated with greater general psychopathology in a single structural network (out of 18 brain-wide structural covariance networks) comprising the precuneus and temporoparietal junction; however, this association did not survive sensitivity analyses (i.e., controlling for maternal education and excluding participants on psychotropic medication) (Kaczkurkin et al., 2019). Another study of the PNC found no evidence of an association with global cortical thickness, whilst follow-up univariate analyses (not controlling for global thickness) found that general psychopathology was negatively associated with cortical thickness specifically within the cuneus, fusiform, postcentral, precentral, precuneus, superior parietal, and transverse temporal regions (Moberget et al., 2019). In contrast to research in youths, global cortical thickness was significantly negatively associated with general psychopathology in midlife participants (age 45) from the Dunedin study (Romer et al., 2021a).

Specific Transdiagnostic Symptom Dimensions.

Internalizing. Internalizing was not associated with global cortical thickness in three studies of preadolescents from the ABCD cohort at baseline (Mewton et al., 2022a; Romer et al., 2023; Modabbernia et al., 2022) or longitudinally across the first two follow-ups (Romer et al., 2023). However, lower global cortical thickness at baseline did predict steeper reductions in Internalizing across the first three waves of the ABCD study (Romer et al., 2023). Follow-up analyses revealed that this association was driven by cortical thickness within 16 (of 68) parcellated brain regions (corrected for global cortical thickness). In the PNC (ages 8–21), anxious-misery showed no association with cortical thickness across 18 brain-wide structural networks in youths (ages 8–21)

(Kaczkurkin et al., 2019). In addition, the fear dimension was negatively associated with cortical thickness in 13 structural networks; however, these associations were no longer significant when controlling for global cortical thickness (Kaczkurkin et al., 2019). In contrast, Internalizing was significantly negatively associated with global cortical thickness at midlife (age 45) (Romer et al., 2021a).

Externalizing. Externalizing was not associated with global cortical thickness in three studies of preadolescents from the ABCD study at baseline (Mewton et al., 2022a; Romer et al., 2023; Modabbernia et al., 2022) or longitudinally across the first three waves of data collection, (Romer et al., 2023) nor with any structural covariance network (across 18 brain-wide networks) in participants aged 8–22 from the PNC (Kaczkurkin et al., 2019). Global cortical thickness was, however, negatively associated with externalizing at midlife (age 45) in the Dunedin Study (Romer et al., 2021a).

Thought Disorder. Global cortical thickness was not associated with the thought disorder dimension in preadolescents (using baseline data from the ABCD study) (Mewton et al., 2022a). Similarly, a psychosis dimension showed no association with global cortical thickness (Moberget et al., 2019) or with regional cortical thickness across 18 brain-wide structural covariance networks (Kaczkurkin et al., 2019) in two studies of youths (ages 8–23) from the PNC. However, global cortical thickness was negatively associated with thought disorder symptoms in midlife participants from the Dunedin study (Romer et al., 2021a).

Neurodevelopmental. The neurodevelopmental dimension was not associated with global cortical thickness in two studies of ABCD participants, at baseline (Romer et al., 2023; Modabbernia et al., 2022) or across the first two follow-ups (Romer et al., 2023).

Detachment. The detachment dimension was not associated with global cortical thickness in two studies of ABCD participants, at baseline (Romer et al., 2023; Modabbernia et al., 2022) and across the first two follow-ups (Romer et al., 2023).

Somatic. The somatic dimension showed no association with global cortical thickness at baseline (or across the first two follow-ups) in ABCD participants, when derived from a higher-order model (Romer et al., 2023) and a correlated-factors model (Modabbernia et al., 2022) but was *positively* associated when derived from ICA (Modabbernia et al., 2022).

Surface area.

General Psychopathology.

Higher general psychopathology predicted lower global surface area (SA) at baseline in preadolescents from the ABCD study (ages 9–10) (Mewton et al., 2022b). Likewise, lower global SA predicted greater levels of general psychopathology at baseline and across the first two follow-up waves of the ABCD study (ages 9–12) (Romer et al., 2023). In contrast, global SA was not associated with general psychopathology at midlife (age 45) (Romer et al., 2021a).

Specific Transdiagnostic Symptom Dimensions.

Internalizing. Internalizing predicted lower global SA at baseline in preadolescents from the ABCD cohort, when derived from higher-order and correlated-factor models (Mewton et al., 2022a; Modabbernia et al., 2022) but not when derived from ICA (Modabbernia et al., 2022). In addition, when global SA was included as a predictor (in another study of ABCD participants), there was no evidence of an association with Internalizing at baseline or across the first two follow-ups (ages 9–12) (Romer et al., 2023). There was also no evidence of an association between global SA and Internalizing at midlife (age 45) (Romer et al., 2021a).

Externalizing. Global SA was negatively associated with externalizing in three studies of preadolescents from the ABCD cohort (Mewton et al., 2022a; Romer et al., 2023; Modabbernia et al., 2022) and in midlife participants from the Dunedin study (Romer et al., 2021a).

Thought Disorder. The thought disorder dimension was negatively associated with global SA in one study of preadolescents (ages 9–10) (Mewton et al., 2022a) but showed no association in midlife (age 45) (Romer et al., 2021a).

Neurodevelopmental. The neurodevelopmental dimension was negatively associated with global SA in ABCD participants when derived from a higher-order model (across the first three waves of data collection) (Romer et al., 2023) and correlated-factors model (at baseline) (Modabbernia et al., 2022) but showed no association when derived from ICA (at baseline) (Modabbernia et al., 2022).

Detachment. The detachment dimension was negatively associated with global SA in two studies of preadolescents from the ABCD cohort, at baseline (Modabbernia et al., 2022) and across the first three waves of data collection (Romer et al., 2023).

Somatic. The somatic symptom dimension was not associated with global SA in two studies of ABCD participants, at baseline (Romer et al., 2023; Modabbernia et al., 2022) or across the first three follow-up waves (Romer et al., 2023).

Gray matter volume.

General Psychopathology.

In preadolescents from the ABCD cohort, general psychopathology predicted lower global GMV at baseline (ages 9–10) (Mewton et al., 2022a) and lower baseline global GMV predicted greater levels (but not the trajectories) of general psychopathology across the first three waves of data collection (ages 9–12) (Romer et al., 2023). In youths from the PNC (ages 8–22), general psychopathology was associated with lower global GMV in one study (Kaczkurkin et al., 2019) and with greater negative deviations from normative cortical volume (but not raw global cortical volume) in another (Parkes et al., 2021). Exploratory whole-brain analyses found that general psychopathology was associated with widespread regionally-specific reductions in GMV across six studies spanning childhood to early adulthood (ages 6–23) (Mewton et al., 2022a; Romer et al., 2023; Kaczkurkin et al., 2019; Parkes et al., 2021; Snyder et al., 2017; Durham et al., 2021).

In contrast, whole-brain analyses in young adults from the DNS (ages 18–22) found that greater general psychopathology was associated with lower GMV in the bilateral lingual gyrus and right intracalcarine regions (of the visual cortex), as well as the left posterior cerebellum, after controlling for total GMV (Romer et al., 2018). Whole-brain analyses (not controlling for global GMV) in midlife participants (age 45) also found that general psychopathology was negatively associated with GMV in relatively few regions (Romer et al., 2021a). Of note, a ROI-based study of participants at midlife (age 45) replicated the negative association between general psychopathology and GMV in the visual cortex but not in the cerebellum (Romer et al., 2021b) (Romer et al., 2018). Similarly, general psychopathology was negatively associated with cerebellar GMV in ROI-based analyses of youths from the PNC (ages 8–22) (Moberget et al., 2019) but failed to replicate in participants at midlife (age 45) (Romer et al., 2021b).

Specific Transdiagnostic Symptom Dimensions.

Internalizing. Internalizing showed few (predominately positive) significant regional associations with GMV in exploratory whole-brain analyses of children (age 6–10) (Snyder et al., 2017). Internalizing predicted lower global GMV at baseline in ABCD participants (ages 9–10), when derived from a higher-order model (Mewton et al., 2022a) but not when derived from ICA or a correlated-factor model (Modabbernia et al., 2022). In whole-brain analyses of ABCD participants (at baseline), Internalizing was associated with widespread reductions in GMV when derived from a higher-order model (none of which remained significant after controlling for global GMV) (Mewton et al., 2022a) and was not associated with any region when derived from a bi-factor model (Durham et al., 2021). In addition, global cortical and subcortical volume did not predict Internalizing (higher-order model) at baseline or across the first two follow-ups (ages 9–12) in a subsequent study of ABCD participants (Romer et al., 2023). In the PNC (ages 8–22), lower global cortical volume (i.e., raw volume and deviations from normative cortical volume) did not predict the anxious-misery dimension and whole-brain analyses revealed relatively few (predominately positive) associations with regional GMV (Parkes et al., 2021). In contrast, the

anxious-misery dimension predicted increased global GMV and was positively associated with GMV in 17 (out of 18) brain-wide structural networks (none of which remained significant after controlling for global GMV) in another study of the same sample (Kaczkurkin et al., 2019). Also in the PNC, lower global cortical volume and greater negative deviations from normative cortical volume predicted higher scores on the fear dimension (Parkes et al., 2021). Follow-up whole--brain analyses (not controlling for global GMV) also found that the fear dimension was associated with lower GMV in relatively few regions. Similarly, the fear dimension (when included as a predictor) was negatively associated with GMV in only eight out of 18 brain-wide structural covariance networks (none of which remained significant after controlling for global GMV) in the PNC (Kaczkurkin et al., 2019). In midlife (age 45), whole-brain analyses (not controlling for global GMV) revealed associations between Internalizing and only four anatomical regions (all of which were shared across other symptom factors) (Romer et al., 2021a).

Externalizing. Externalizing showed relatively few regional associations with GMV based on whole-brain analyses of a childhood community sample (ages 6–10) (Snyder et al., 2017). When derived from a higher-order model, externalizing predicted lower global GMV at baseline in ABCD participants (ages 9–10) (Mewton et al., 2022a) and lower global GMV predicted greater externalizing at baseline and across the first two follow-ups (ages 9–12) (Romer et al., 2023). However, there was no evidence of association with global GMV when externalizing was derived from ICA or a correlated-factors model in baseline ABCD data (Modabbernia et al., 2022). In addition, whole-brain analyses of ABCD participants (at baseline) found that externalizing predicted widespread regional reductions in GMV; however, no associations remained significant after controlling for global GMV (Mewton et al., 2022b). In the PNC (ages 8–22), global cortical volume (i.e., raw cortical volume and deviations from normative cortical volume) did not predict externalizing (Parkes et al., 2021). Follow-up whole-brain analyses found negative associations between externalizing and GMV in relatively few regions. Similarly, another study of the PNC found that externalizing predicted lower cortical volume in only two (i.e., superior parietal and fusiform cortices) of 18 brain-wide structural networks and these associations did not survive sensitivity analyses (controlling for maternal education and psychotropic medication use) (Kaczkurkin et al., 2019). Lastly, whole-brain analyses of midlife participants (age 45) also found relatively few associations between externalizing and regional GMV (Romer et al., 2021a).

Thought Disorder. The thought disorder dimension was negatively associated with global cortical volume in preadolescents from the ABCD study (ages 9–10) (Mewton et al., 2022b). Follow-up analyses revealed widespread reductions in regional GMV, none of which remained significant after controlling for global GMV. In the PNC (ages 8–22), lower global cortical volume (i.e., lower raw volume and greater negative deviations from normative cortical volume) predicted greater scores on a psychosis-positive (but not psychosis-negative) dimension (Parkes et al., 2021). Follow-up whole-brain analyses revealed few associations between psychosis-positive or psychosis-negative dimensions. Also in the PNC, a general psychosis dimension did not predict GMV in any of 18 brain-wide structural networks. Similarly, whole-brain analyses of participants at midlife (age 45) found few associations between thought disorder symptoms and regional GMV (Romer et al., 2021a).

Neurodevelopmental. When derived from a higher-order model, the neurodevelopmental dimension predicted lower global GMV at baseline in ABCD participants (ages 9–10) (Mewton et al., 2022a) and lower global cortical and subcortical GMV predicted higher scores on the neurodevelopmental dimension at baseline and across the first two follow-ups (ages 9–12) (Romer et al., 2023). However, there was no evidence of association with global GMV when the neurodevelopmental dimension was derived from ICA or a correlated-factors model using baseline ABCD data (Modabbernia et al., 2022).

Detachment. The detachment dimension was negatively associated with global cortical and subcortical volume across the first three waves of the ABCD study when derived from a higher-order model (Romer et al., 2023) but showed no association at baseline when derived from a correlated-factor model or ICA (Modabbernia et al., 2022).

Somatic. Two studies found no association between the somatic dimension and global GMV in ABCD participants at baseline (Romer et al., 2023; Modabbernia et al., 2022), or across the first two follow-up waves (Romer et al., 2023).

3.4.2. White matter microstructure

General Psychopathology.

Lower global fractional anisotropy (FA) (i.e., average fractional anisotropy across 12 white matter tracts) was associated with higher general psychopathology in children (ages 6–10) from the Generation R cohort (Neumann et al., 2016). In ABCD participants (ages 9–10), there were no significant associations between general psychopathology and FA in any of 17 bilateral white matter (WM) tracts following FDR correction (Cardenas-Iniguez et al., 2022). In contrast, exploratory whole-brain analyses in young adults from the DNS (ages 18–22) found that general psychopathology predicted lower FA specifically within the bilateral pons, when controlling for global FA (Romer et al., 2018). Follow-up ROI analyses (of white matter tracts within the pons and cerebellum) found that greater general psychopathology predicted lower FA in the right and left lemniscus, as well as the left superior peduncle (again controlling for whole-brain FA). The association between general psychopathology and lower FA in the pons (but not the cerebellum) when controlling for global FA, was subsequently replicated in participants at midlife (age 45) (Romer et al., 2021b). Analyses using an alternative model (not controlling for global FA) found that general psychopathology predicted lower FA in the medial peduncle of the cerebellum (Neumann et al., 2020). Lastly, general psychopathology showed no evidence of association with global medial diffusivity in children (ages 6–10) (Neumann et al., 2020) or with any of 17 bilateral WM tracts in preadolescents (ages 9–10) (Cardenas-Iniguez et al., 2022).

Specific Transdiagnostic Symptom Dimensions.

Internalizing. Global FA was not associated with Internalizing in children (ages 6–10) from the Generation R cohort (Neumann et al., 2020). In ABCD participants (ages 9–10), Internalizing was negatively associated with global FA when derived from a correlated-factor model but not from ICA (Modabbernia et al., 2022) and showed no association with any of 17 WM tracts when measured using a bi-factor model (Cardenas-Iniguez et al., 2022). ROI-based analyses in young adults (ages 18–22) found that Internalizing was associated with lower pons FA (Romer et al., 2018). Internalizing showed no association with mean diffusivity (across three studies) (Modabbernia et al., 2022; Cardenas-Iniguez et al., 2022; Neumann et al., 2020), or axial and radial diffusivity (across two studies) (Modabbernia et al., 2022; Neumann et al., 2020), spanning childhood (ages 6–10) and preadolescence (ages 9–10).

Externalizing. Externalizing was positively associated with global FA in one study of children (ages 6–10) (Neumann et al., 2020). In preadolescents (ages 9–10), global FA was not associated with two measures of externalizing, derived from a correlated-factor model and ICA (Modabbernia et al., 2022). ROI-based analyses in young adults (ages 18–22) found no association between externalizing and pons FA (Romer et al., 2018). Externalizing (bi-factor model) was negatively associated with global radial diffusivity in children (ages 6–10) (Neumann et al., 2020) but showed no association in preadolescents from the ABCD study when derived from a correlated-factor model and ICA (ages 9–10) (Modabbernia et al., 2022). There was no evidence of association between externalizing and mean or axial diffusivity across two studies of children (ages 6–10) and preadolescents (ages 9–10) (Modabbernia et al., 2022; Neumann et al., 2020).

3.5. Functional neuroimaging studies

3.5.1. Functional connectivity

General Psychopathology.

Four studies investigated the relationship between general psychopathology and functional connectivity in preadolescents (ages 9–10) from the ABCD cohort (at baseline) (Lees et al., 2021; Karcher et al., 2021; Hong et al., 2023; Sripada et al., 2021). General psychopathology was measured using higher-order (Lees et al., 2021), bi-factor (Sripada et al., 2021), and one-factor models (Karcher et al., 2021; Hong et al., 2023). Higher general psychopathology was associated with lower functional connectivity within the default mode network (DMN) across three studies (Karcher et al., 2021; Hong et al., 2023; Sripada et al., 2021) and showed no association in one study (using a higher-order model) (Lees et al., 2021). General psychopathology was also associated with lower functional connectivity within the dorsal attention network (DAN) across three studies (Lees et al., 2021; Hong et al., 2023; Sripada et al., 2021) but showed no association in one (using a one-factor model) (Karcher et al., 2021). General psychopathology was associated with higher functional connectivity within the visual network (VIS) (Hong et al., 2023) in one study (one-factor model), with lower functional connectivity in another (bi-factor model) (Sripada et al., 2021) and showed no association in the remaining two studies (Lees et al., 2021; Karcher et al., 2021). No association was found for functional connectivity within the cingulo-opercular (CON), cingulo-parietal (CPN), salience (SAL), ventral attention (VAN), auditory (AUD), and somatomotor hand (SMH) networks across all four studies (Lees et al., 2021; Karcher et al., 2021; Hong et al., 2023; Sripada et al., 2021). There was also no evidence of association between general psychopathology and within-network connectivity in an 'unassigned' network across three studies (Karcher et al., 2021; Hong et al., 2023; Sripada et al., 2021), or with within-network connectivity in the cerebellum across two studies (Lees et al., 2021; Sripada et al., 2021).

Two studies of ABCD participants found that general psychopathology was associated with higher connectivity between the DMN and DAN (Lees et al., 2021; Hong et al., 2023) and between the VAN and frontoparietal (FPN) networks (Lees et al., 2021; Sripada et al., 2021). One study found that general psychopathology significantly increased the proportion of variance explained in functional network connectivity between the DMN and VAN (relative to a baseline model with only covariates); however, this was not replicated in a hold-out sample of ABCD participants (Karcher et al., 2021). An additional study found that general psychopathology was associated with lower connectivity between the DMN and VAN networks (Sripada et al., 2021). Several other associations with between-network connectivity were identified in only a single study and showed no association in the remaining studies (Appendix B, Table S6). Lastly, in young adults from the DNS (ages 18–22), connectome-wide analyses found that general psychopathology was associated with functional connectivity in four regions located within the visual network, including the left lingual gyrus, right middle occipital gyrus, and two parcels within the left middle occipital gyrus (Elliott et al., 2018). Follow-up analyses revealed that general psychopathology was associated with higher connectivity between the visual association cortex and DMN and between the visual association cortex and FPN. In contrast, general psychopathology was associated with lower connectivity between the visual association cortex and somatomotor network.

Specific Transdiagnostic Symptom Dimensions.

Four studies investigated the relationship between specific transdiagnostic symptom dimensions and within- and between-network functional connectivity. However, no significant associations were reported across more than one study aside from a single finding. Specifically, the neurodevelopmental symptom dimension was associated with lower connectivity within the DMN in the ABCD cohort (ages 9–10) (Karcher et al., 2021) and participants from the PNC (ages 8–22) (Modabbernia et al., 2022).

3.6. Other analyses

There were several relationships between transdiagnostic symptom dimensions and biological variables that were only investigated in a single study and are not reported here (Tables S5-7). There were three functional neuroimaging studies that examined different brain regions and experimental tasks (i.e., n-back, emotional n-back, and an economic choice lottery task) (Lees et al., 2021; Shanmugan et al., 2016; Kim-Spoon et al., 2021). Other studies included analyses of regional cerebral blood flow, (Kaczkurkin et al., 2018) PGSs and brain structure, (Fernandez-Cabello et al., 2022) multimodal DTI measures, (Alnæs et al., 2018) and brain age derived from multiple structural neuroimaging measures (Caspi et al., 2020). Finally, one study examined the relationship between brain structure and a latent measure of behavioural disinhibition (van Rooij et al., 2021).

4. Discussion

This systematic review aimed to synthesize evidence from research investigating the biological correlates of latent transdiagnostic dimensions of psychopathology in the general population, across the lifespan. The following section summarises key findings by broad biological domain (i.e., genomic, neuroimaging) and phenotype (i.e., general psychopathology and specific transdiagnostic symptom dimensions). Implications for research investigating associations across the lifespan, as well as potential developmental and age-specific associations emerging from the included studies, are discussed. Interpretations of general psychopathology in the context of genomic and neurobiological evidence are discussed. Methodological issues are highlighted, including those which point to the need for caution in interpretation and those which may explain some of the heterogeneity in results observed across included studies. Finally, directions for future research are provided and limitations of the current review are addressed.

4.1. Genomic research studies

General psychopathology.

General psychopathology was non-specifically associated with genetic risk for a wide range of psychiatric disorders and maladaptive traits in the general population. Several disorder- and trait-specific PGSs were significantly positively associated with general psychopathology across multiple studies (i.e., ADHD, neuroticism, depression, schizophrenia, anxiety, and PTSD). Additional studies examined associations between general psychopathology and transdiagnostic PGSs that reflect genetic risk for multiple psychiatric disorders (i.e., 'polygenic p-factors). These genomic p-factors emerged across different samples (TEDS, UK Biobank, HRS) and developmental periods (childhood to adolescence and midlife to older adulthood) and were consistently found to predict phenotypic measures of general psychopathology (Allegrini et al., 2020; Grotzinger et al., 2019; Gard et al., 2021). The results of included studies align with twin and molecular genetic research demonstrating evidence of widespread pleiotropy and shared genetic associations across psychiatric disorders (Waszczuk et al., 2020; Martin et al., 2018; Wray et al., 2014). They also provide compelling evidence that estimates of general psychopathology reflect an underlying genetic liability towards diverse manifestations of mental illness, supporting the biological validity of general psychiatric phenotypes.

Specific transdiagnostic symptom dimensions.

Specific transdiagnostic symptom dimensions were also significantly associated with a wide range of PGSs in the general population. However, positive associations among these dimensions showed a greater level of specificity than those found for general psychopathology. That is, associations were predominately found for PGSs that capture genetic risk for disorders and traits which form part of their constituent symptom dimensions. For example, internalising was mostly positively

associated with PGSs that reflect risk for internalising-related disorders and traits, such as depression (Riglin et al., 2020; Pat et al., 2022; Musci et al., 2016; Jermy et al., 2022) and neuroticism (Chen et al., 2022; Cuevas et al., 2021). Conversely, externalising was mostly associated with externalising-related PGSs (e.g., ADHD, disinhibition, number of sexual partners, adventurousness) (Waszczuk et al., 2021; Pat et al., 2022; Li, 2019). These findings are consistent with hierarchical models of psychopathology, which predict that genetic variants associated with specific symptoms/syndromes (e.g., depression) captured by a given dimension (e.g., internalising) will be more strongly associated with that dimension than with others (e.g., externalising) (Waszczuk et al., 2020). However, this was not entirely consistent across exposure-outcome pairings (e.g., anxiety-PGSs were not associated with internalising-related phenotypes across multiple studies) and further research is needed to confirm this pattern of association (Chen et al., 2022; Cuevas et al., 2021).

The included studies also found evidence of shared and unique genetic associations across specific symptom dimensions. For instance, PGSs that were significantly associated with a given specific symptom dimension were consistently also associated with general psychopathology across studies, indicating shared genetic influences. There was *some* evidence of shared genetic associations across specific symptom dimensions (e.g., depression-PGSs were positively associated with internalising, externalising and neurodevelopmental dimensions) (Pat et al., 2022) but these were only found *within* individual studies. In addition, dimension-specific associations were reported *within* several individual studies (Riglin et al., 2020; Waszczuk et al., 2021; Lahey et al., 2022; Chen et al., 2022) but there was limited evidence of unique and replicable associations between specific symptom dimensions and PGSs found across studies. Notable exceptions to this include consistent negative associations between internalising and ADHD-PGSs (Riglin et al., 2020; Waszczuk et al., 2021; Lahey et al., 2022; Chen et al., 2022) and positive associations between internalizing and PGSs for intelligence and educational attainment in early development (Waszczuk et al., 2021; Chen et al., 2022). Several quantitative genetic studies have demonstrated evidence of unique genetic influences on higher-order transdiagnostic symptom dimensions, (Lahey et al., 2011; Waldman et al., 2016) subdimensions, (Waszczuk et al., 2014; Kendler et al., 2003) and measures of specific psychiatric symptoms or syndromes (Kendler et al., 2013). Research using genomic structural equation modeling has also found evidence of genetic variants that are uniquely associated with transdiagnostic dimensions when defined by genetic correlations rather than symptom- or disorder-level correlations (Grotzinger et al., 2022). As such, the relative lack of dimension-specific associations found across studies included in the review may reflect certain methodological limitations rather than an absence of unique genetic associations across different levels of the structural hierarchy.

For instance, case-control GWASs based on categorically defined psychiatric phenotypes likely capture genetic variants that are highly pleiotropic. As such, PGSs constructed from these studies may capture non-specific variance in psychopathology and therefore lack the specificity needed to identify dimension-specific associations (Waszczuk et al., 2021). Future GWASs investigating phenotypes at different levels of the symptom hierarchy (e.g., internalising, externalising) may yield more precise PGSs that are better able to capture unique associations (Waszczuk et al., 2023). Some heterogeneity in the results may also be explained by different approaches to the construction of PGSs themselves (Appendix B, Table S5). For example, PGSs for same phenotype can be constructed using the summary statistics from different GWASs, which may identify different genetic variants associated with the target phenotype. Discovery GWASs can also differ substantially in sample size (across GWASs of the same phenotype and across GWASs of different phenotypes), with lower sample sizes limiting power to detect effects of different genetic variants and lowering the accuracy of a given PGS (Andlauer and Nöthen, 2020). Researchers may also adopt different p-value thresholds in deciding which genetic variants were significantly associated with a given phenotype in discovery GWASs (Andlauer and Nöthen, 2020). These and other factors impact the composition of PGSs and may explain why some significant associations failed to replicate across studies.

4.2. Neuroimaging research studies

4.2.1. Gray matter structure

General psychopathology.

General psychopathology was predominately associated with broad, non-specific reductions in gray matter structure across the included studies. For instance, the included studies found evidence that general psychopathology was significantly negatively associated with global measures of CT, (Romer et al., 2021a) SA, (Mewton et al., 2022a; Romer et al., 2023) and GMV (Mewton et al., 2022a; Romer et al., 2023; Kaczkurkin et al., 2019; Parkes et al., 2021). Whole-brain analyses also tended to reveal evidence of widespread regional associations across each of these metrics (Mewton et al., 2022a; Romer et al., 2023, 2021a; Snyder et al., 2017; Durham et al., 2021). Importantly, regional associations tended to be largely or entirely non-significant after controlling for global effects, further suggesting that reductions in gray matter structure are widely distributed (Mewton et al., 2022a; Romer et al., 2023; Kaczkurkin et al., 2019; Durham et al., 2021).

These results provide compelling evidence that shared neurobiological vulnerabilities underpin diverse manifestations of psychopathology in the general population. In line with this, alterations in gray matter structure have been independently linked to various psychiatric disorders and cross-disorder research demonstrates that these associations are largely shared across diagnostic categories (Goodkind et al., 2015; Opel et al., 2020). The predominant pattern of global/widespread associations also aligns with theoretical predictions that the biological correlates of higher-order symptom dimensions will show broad, non-specific associations with different biological mechanisms and processes (Zald and Lahey, 2017). However, evidence of global alteration does not necessarily imply that all brain regions are equally affected. Meta-analytic research indicates that brain-wide patterns of covariance in gray matter structural networks that are altered across different disorders show non-random organization and may be driven by reductions within specific large-scale networks, including prefrontal and temporal regions (Hettwer et al., 2022). Consistent with these findings, two ROI-based analyses found that general psychopathology was associated with lower GMV in prefrontal and temporal regions (Parkes et al., 2021; Snyder et al., 2017) and functional imaging research pointed to a central role of disrupted connectivity in the DMN (which comprises both the prefrontal cortex and medial temporal lobe).

Specific Transdiagnostic Symptom Dimensions.

Specific symptom dimensions were similarly associated with broad, non-specific reductions in gray matter structure across various metrics. This included negative global and regional associations with CT, (Romer et al., 2021a) SA, (Mewton et al., 2022a; Romer et al., 2023, 2021a; Modabbernia et al., 2022) and GMV (Mewton et al., 2022a; Romer et al., 2023; Kaczkurkin et al., 2019; Parkes et al., 2021). However, some studies reported fewer regionally-specific associations with specific symptom dimensions compared to general psychopathology (Kaczkurkin et al., 2019; Parkes et al., 2021; Snyder et al., 2017). Moreover, regional associations with a given symptom dimension tended to overlap with those found for general psychopathology and/or other specific symptom dimensions. There was evidence of dimension-specific associations *within* several studies, specifically between: fear and CT; (Kaczkurkin et al., 2019) internalizing and CT; (Romer et al., 2023) externalizing and SA; (Romer et al., 2021a) internalizing and GMV; (Snyder et al., 2017) and anxious-misery and GMV (Kaczkurkin et al., 2019; Parkes et al., 2021). However, only one of these associations was reported across more than a single study.

It is difficult to draw conclusions regarding the lack of dimension-specific associations found across studies given limited research and

substantial methodological differences (e.g., sample size, latent variable models, measurement of brain structure). More consistent evidence of association may emerge from studies attempting to directly replicate existing research. Alternatively, the lack of dimension-specific associations may indicate that brain structural alterations are shared across higher-order dimensions (e.g., general psychopathology, internalizing, externalizing), whilst other factors (e.g., environmental) contribute more to differential symptom expression. However, though more specific than general psychopathology, many of the higher-order symptom dimensions included in these studies capture a broad (i.e., heterogeneous) range of psychiatric symptoms. Unique biological correlates may be more likely to emerge at lower levels of the symptom hierarchy. For example, the relationship between internalizing and GMV showed mixed results across studies, including non-significant, (Romer et al., 2023; Durham et al., 2021) negative, (Mewton et al., 2022a) and positive associations (Snyder et al., 2017). However, two studies examined the internalizing subdimensions of anxious-misery and fear in the PNC and both found that fear was negatively associated with GMV whilst anxious-misery was positively associated (Kaczkurkin et al., 2019; Parkes et al., 2021). These divergent associations among lower-order subdimensions may explain the inconsistencies between studies investigating internalizing more broadly (i.e., contrasting patterns of association between lower-order subdimensions may effectively cancel each other out); however, this interpretation should be considered cautiously given that it is based on only two studies of the same sample.

4.2.2. White matter microstructure

General psychopathology.

Few studies investigated the relationship between white matter microstructure and transdiagnostic symptom dimensions. Studies of children and preadolescents (ages 6–10) found that general psychopathology was negatively associated with global FA (Neumann et al., 2020) and showed no evidence of regionally-specific associations (Cardenas-Iniguez et al., 2022; Neumann et al., 2020). In contrast, research in young adults (18−22) found that general psychopathology was associated with reduced FA specifically within the bilateral pons, after controlling for global effects (Romer et al., 2018). This association was subsequently replicated in a sample of participants at midlife (age 45) (Romer et al., 2021b) but not in childhood (ages 6–10) (Neumann et al., 2020). These findings *may* indicate that regionally-specific associations with FA emerge later in development, perhaps due to neurodegeneration of certain white matter pathways as a consequence of prolonged exposure to psychopathology. However, further research is needed to replicate these findings before meaningful conclusions can be drawn.

Specific transdiagnostic symptom dimensions.

Associations with specific transdiagnostic symptom dimensions were more mixed. Internalizing was negatively associated with global but not regional FA in a single study (Neumann et al., 2020). However, other analyses found no evidence of global (Modabbernia et al., 2022) or regional associations (Cardenas-Iniguez et al., 2022; Neumann et al., 2020). Conversely, externalizing was positively associated with global and regional FA in a single study (Neumann et al., 2020) but showed no association with either global (Modabbernia et al., 2022) or regional FA in others (Cardenas-Iniguez et al., 2022). Regional associations were not statistically significant for both phenotypes in the one study that controlled for global effects, (Neumann et al., 2020) which may indicate a distributed effect. The positive association observed between externalizing and FA is intriguing, particularly as externalizing and related disorders have previously been linked to greater levels of FA (Cardenas et al., 2013; Teeuw et al., 2022). However, as above, further research is needed to replicate this finding.

4.2.3. Functional connectivity

General psychopathology.

General psychopathology was associated with widespread alterations in connectivity within- and between several large-scale networks across the included studies. However, the findings discussed below (i.e., those reported across multiple studies) were all from cross-sectional studies of ABCD participants and as such, the extent to which they generalize to different samples and developmental periods is unclear. In terms of within-network connectivity, the strongest evidence was found for *lower* connectivity within the DMN and DAN (Karcher et al., 2021; Hong et al., 2023; Sripada et al., 2021). The DMN represents a network of brain regions that exhibit correlated patterns of activity during rest (i.e., when an individual is not engaged in a particular task or otherwise exposed to some external stimulus) (Raichle, 2015). This network is responsible for various cognitive functions related to internal mental activity (e.g., spontaneous thought) and self-referential mental processes (e.g., self-monitoring, introspection) (Andrews-Hanna, 2012). In contrast, the DAN is involved with various attentional processes and is primarily characterized by its association with top-down control during tasks requiring focused attention (Corbetta and Shulman, 2002; Fox et al., 2005). As such, findings from the included studies may indicate that general psychopathology is broadly associated with alterations in functional networks dedicated to both internally- and externally-focused cognitive processes. Importantly, impaired cognitive function (e.g., attentional control) and dysregulated thought are core features of many psychiatric disorders. Interestingly, the DMN neurotypically exhibits 'anti-correlations' (i.e., opposing patterns of activity between networks) with other control networks, including the DAN (Fox et al., 2005). Reduced negative correlations between the two networks indicate further disruption to the balance of networks supporting internally- and externally-focused cognition and have also been implicated in several disorders (Patriat et al., 2016; Hu et al., 2017; Posner et al., 2016; Owens et al., 2020a). In line with this, two included studies found that general psychopathology was associated with *greater* connectivity between the DMN and DAN (Lees et al., 2021; Hong et al., 2023). Reduced negative correlations between these networks may serve as a transdiagnostic feature of broad mental illness; however, additional research is needed to replicate these findings (particularly across other samples and age groups).

4.3. Biological associations with transdiagnostic symptom dimensions across the lifespan

As noted, the majority of included studies were restricted to cross-sectional analyses of youth (i.e., childhood to young adulthood). This focus on younger samples and the relative lack of longitudinal analyses makes it difficult to draw conclusions about developmental associations. However, some findings may reflect age-specific differences and warrant further investigation in future research.

4.3.1. Genomic research studies

Longitudinal genomic studies were conducted only in childhood and adolescent samples (ages 7–16) (Allegrini et al., 2020; Riglin et al., 2020; Lahey et al., 2022; Chen et al., 2022). There was evidence of age-specific differences in genetic associations with different symptom dimensions *within* most of these studies (Riglin et al., 2020; Lahey et al., 2022; Chen et al., 2022). Two of these studies revealed PGSs that became significantly associated with a given symptom dimension in a genetically coherent manner in later developmental periods (Riglin et al., 2020; Chen et al., 2022). For example, depression-PGSs were not associated with internalising in childhood but were positively associated in adolescence (Riglin et al., 2020). These findings align with epidemiological research demonstrating increases in the prevalence of internalising-related disorders between childhood and adolescence, which suggest a developmental role in the activation of genetic influences on internalising during puberty (Moffitt et al., 2007). Of note, PGSs were primarily constructed using summary statistics from GWASs of adult samples, which may capture genetic risk that emerges in later developmental periods, potentially explaining why positive associations only emerged in later developmental periods across these studies

(Allegrini et al., 2022). Future research should examine these associations using PGSs from GWASs of similar age groups and explicitly test whether PGSs show greater genetic coherence with specific symptom dimensions in later development.

Some results *across* studies also point to potential developmental associations. For example, general psychopathology showed some evidence of developmental stability in its association with general PGSs (i.e., polygenic p-factors) (Allegrini et al., 2020; Grotzinger et al., 2019; Gard et al., 2021) and neuroticism-PGSs (Gard et al., 2021; Waszczuk et al., 2021; Chen et al., 2022; Jones et al., 2018). Both of these PGSs were consistently positively associated with general psychopathology across different development periods, including midlife to older adulthood. In contrast, ADHD-PGSs may show developmental differences in association with general psychopathology. ADHD-PGSs were positively associated with general psychopathology across six studies (spanning childhood to adolescence) (Riglin et al., 2020; Waszczuk et al., 2021; Pat et al., 2022; Lahey et al., 2022; Brikell et al., 2020; Chen et al., 2022) but showed no association in a sample of midlife to older adult participants (Gard et al., 2021). Meta-analytic evidence indicates that ADHD declines significantly in adulthood (Faraone et al., 2006) and age-specific differences in the prevalence of ADHD have been observed between younger elderly adults and older elderly adults (Michielsen et al., 2012). As such, this lack of association may indicate age-specific declines in the contribution of genetic risk for ADHD to the general expression of psychopathology in later life. However, the lack of association between ADHD-PGSs and general psychopathology in older adults was only found in a single study. It should also be noted that the ADHD-PGSs for this study were constructed using summary statistics from a GWAS that predominately used childhood samples (Demontis et al., 2019) and thus, these PGSs may simply show less association in older samples.

4.3.2. *Structural neuroimaging studies*

Only one study examined the relationship between brain structure and transdiagnostic symptom dimensions longitudinally, (Romer et al., 2023) finding that lower global CT in preadolescence was uniquely associated with steeper reductions in (but not the mean levels of) internalizing across time (ages 9–12). Across studies, general psychopathology was consistently negatively associated with cortical SA but not CT (Mewton et al., 2022a; Romer et al., 2023) in ABCD participants (ages 9–12). However, the inverse was found in a single study of participants at midlife from the Dunedin Study (age 45), such that general psychopathology was negatively associated with CT but not SA (Romer et al., 2021a). This pattern of association was largely consistent with that found for specific symptom dimensions (Mewton et al., 2022a; Romer et al., 2023; Modabbernia et al., 2022).

These two metrics (CT, SA) are genetically distinct components of GMV, which follow different developmental trajectories and undergo significant structural changes throughout childhood and early adulthood. CT tends to peak in childhood before decreasing linearly throughout childhood and adolescence, whilst surface area reaches its peak in preadolescence, plateaus, and then decreases subtly across adolescence and early adulthood (Tamnes et al., 2017; Wierenga et al., 2014). In contrast, midlife represents a period of relative stability in terms of cortical structure, where neurodegenerative and ageing processes become the predominate drivers of change (Peters, 2006; Oschwald et al., 2019). The negative association between SA and general psychopathology in preadolescence may therefore reflect disruptions to normative neurodevelopmental processes (which may precede or follow from the onset of psychopathology). Conversely, the negative association between CT and general psychopathology may reflect accelerated ageing or neurodegenerative processes that follow from prolonged exposure to mental illness. This is supported by another included study, which found that general psychopathology was associated with greater brain age (calculated from various indices of brain structure) at age 45 (Caspi et al., 2020). Further research is needed to replicate this association at midlife and longitudinal research should specifically examine whether the relationship between brain structure (i.e., SA and CT) and general psychopathology changes across development.

4.4. *Interpretations of general psychopathology in the context of genomic and neurobiological research*

The interpretation of general and specific transdiagnostic symptom dimensions is the subject of ongoing debate in the literature. Prominent substantive interpretations suggest that general psychopathology reflects trait negative emotionality (e.g., neuroticism), impaired emotion regulation, cognitive deficits, and/or disordered thought processes (Smith et al., 2020; Caspi and Moffitt, 2018b). Each of these constructs can be broadly captured under the domains of impaired emotional functioning (e.g., negative emotionality, impaired regulation of emotion) and impaired cognitive functioning (e.g., cognitive deficits, disordered thought processes), which aligns with a more parsimonious and all-encompassing interpretation offered for general psychopathology i.e., that it reflects general *impairment (*Smith et al., 2020*)*. In line with this interpretation, we propose that a vast array of genetic variants act pleiotropically to predispose individuals to general impairments in the structural and functional neural mechanisms supporting cognitive and emotional functioning, which in turn contribute to the expression of general psychopathology. Individual differences in the type (e.g., specific SNPs) and number of contributing genetic variants (as well as in environmental factors) allow for variation in the nature and severity of alterations to brain structure and function, which may account for the observed variation in levels of general psychopathology between individuals.

Several findings from the included studies support the interpretation that general psychopathology reflects impairment in cognitive and emotional functioning. For example, general psychopathology was consistently inversely associated with PGSs for educational attainment and intelligence (Waszczuk et al., 2021; Chen et al., 2022). In terms of trait- and disorder-specific associations, the strongest evidence was found for neuroticism- and ADHD-PGSs. PGSs for neuroticism capture genetic risk for trait negative emotionality and were consistently positively associated with general psychopathology across four studies (Gard et al., 2021; Waszczuk et al., 2021; Chen et al., 2022; Jones et al., 2018). ADHD-PGSs were positively associated with general psychopathology across six of the included studies (Riglin et al., 2020; Waszczuk et al., 2021; Pat et al., 2022; Lahey et al., 2022; Brikell et al., 2020; Chen et al., 2022). ADHD is characterised by marked deficits in cognitive (e.g., attentional control, working memory, response-inhibition) and emotional functioning (e.g., emotion regulation, emotion recognition, negative emotionality). In general population samples, ADHD-PGSs have been found to be associated with impaired cognitive function (independently of their association with ADHD symptoms) (Stergiakouli et al., 2016; Martin et al., 2015) and trait negative emotionality (Du Rietz et al., 2018). As such, ADHD-GWASs may be capturing the pleiotropic effects of genetic variants associated with broader domains of cognitive and emotional impairment, in addition to more specific variance at the level of lower-order dimensions (e.g., externalizing, neurodevelopmental) or specific disorders (e.g., ADHD-specific variance).

These and other genetic variants associated with the expression of mental illness likely exert their influence indirectly via their impact on early brain development and subsequent impact on cognitive and emotional functioning. It is well-established that cognitive and emotional processes emerge from complex and co-ordinated interactions among large-scale structural and functional brain networks, which are themselves under genetic influence (Rasch et al., 2010; P.O.F. T. Guimarães et al., 2022; Elliott et al., 2019a). It is also important to note that cognitive and emotional functioning are not distinct from one another but are inextricably connected and supported by shared structural and functional brain correlates (Pessoa, 2008; Okon-Singer et al., 2015). Indeed, many aspects of impaired emotional functioning (e.g.,

excessive rumination, maladaptive information processing/recall, poor emotional regulation) are connected to important facets of cognitive function (e.g., attentional control, response inhibition).

Interestingly, associations between greater cognitive function and brain structure (i.e., CT and SA) essentially reflect the inverse of associations found between greater general psychopathology and brain structure in the included studies. For example, greater cognitive function is associated with larger SA but not CT in preadolescents and with greater CT in midlife (Schnack et al., 2015). Genetic influences on cognitive function (e.g., PGSs for educational attainment) have likewise been found to be positively associated with global brain volume in population-based samples (Elliott et al., 2019b) and specifically with global volume and SA but not CT in young adults (Mitchell et al., 2020). Similarly, trait negative emotionality has been linked to smaller global brain volume and widespread reductions in white matter microstructure (Bjørnebekk et al., 2013) and GWASs have demonstrated negative genetic correlations between neuroticism and global SA (Grasby et al., 2020). Finally, functional brain networks that were consistently associated with general psychopathology in the included studies (e.g., the DMN and DAN) are also linked to cognitive and emotional functioning. For example, anti-correlations between the DMN and DAN have consistently been linked to cognitive performance, (Wang et al., 2019; Owens et al., 2020b; Hampson et al., 2010) which aligns with evidence that general psychopathology is associated with greater connectivity between these two networks. High negative emotionality has likewise been linked to alterations in whole-brain functional connectivity (Servaas et al., 2015) and specifically to lower connectivity within the DMN (Li et al., 2022) and DAN, (Simon et al., 2020) which is further consistent with associations found for general psychopathology in the included studies.

4.5. Methodological considerations

4.5.1. Latent variable models

The findings of this review must be interpreted in light of considerable heterogeneity in methodological approaches taken across studies. Most importantly, included studies varied substantially in terms of observable indicators of psychopathology (e.g., assessment scales) and in the statistical models used to extract latent symptom dimensions from those indicators. The most commonly used approach was a bi-factor model, which is consistent with a previous systematic literature review examining risk and protective factors of empirical models of psychopathology in youths aged 10–24 (Lynch et al., 2021). The bi-factor model is distinct from other commonly used factor analytic approaches, such as correlated-factor and higher-order models (Markon, 2019; van Bork et al., 2017). In a correlated-factor model, a given number of latent variables (e.g., internalizing, externalizing) are specified to account for the shared variance among a set of psychiatric indicators (e.g., symptoms). In higher-order models, the set of indicators load onto lower-order factors (as in a correlated factor model) and a higher-order general factor (e.g., general psychopathology) is derived from the variance shared among those lower-order factors. As such, the general factor *explains* the shared variance of a given number of lower-order factors and is only indirectly related to indicators included in the model (Markon, 2019; van Bork et al., 2017). In contrast, bi-factor models include both general and specific (e.g., internalizing, externalizing) factors but the general factor loads directly onto the indicators and all factors within the model are specified to be orthogonal to one another. That is, general and specific factors in a bi-factor model are statistically independent (uncorrelated) and thus, the specific factors explain the shared variance across subsets of indicators (e.g., psychiatric symptoms) that remains *after the effects of the general factor have been removed* (Markon, 2019; van Bork et al., 2017). Bi-factor models are commonly used in studies examining the latent structure of psychopathology because they tend to demonstrate superior goodness of fit (Watts et al., 2019) and ease of interpretation. However, goodness of fit is increasingly recognized to be an insufficient indicator of structural validity and many authors now recommend comparisons across different modelling approaches (Lynch et al., 2021; Forbes et al., 2021).

Although each model is closely related, the interpretation of general and specific factors and the nature of their associations with external (e.g., biological) variables differs substantially depending on which statistical approach is adopted. For example, ADHD-PGSs were positively associated with both externalizing and neurodevelopmental dimensions across multiple studies. However, ADHD-PGSs were only positively associated with externalizing when using a higher-order model (Pat et al., 2022) or when modelling externalizing in isolation within a LGC model (Li, 2019) and there was no evidence of association when using a bi-factor model (Riglin et al., 2020) or otherwise controlling for the effects of general psychopathology (Waszczuk et al., 2021). In contrast, ADHD-PGSs were consistently positively associated with the neurodevelopmental dimension across multiple structural models, including the bi-factor model (Riglin et al., 2020; Waszczuk et al., 2021; Pat et al., 2022). Of note, one study found that the positive association between ADHD-PGSs and the neurodevelopmental dimension was the only significant association to emerge across 22 different PGSs after controlling for general psychopathology (Waszczuk et al., 2021). Consideration of these different modelling approaches suggests that ADHD-PGSs may be more strongly associated with the neurodevelopmental dimension than externalizing. This is also supported by quantitative genetic research, which similarly found that ADHD was significantly correlated with the neurodevelopmental dimension (and no others) after controlling for general psychopathology and that this association was largely driven by genetic effects (Du Rietz et al., 2021).

4.5.2. Genomic methods

Effect sizes were small across the included genomic studies (i.e., >0.15; Supplementary Table S5), which is common in research investigating associations between PGSs and psychiatric phenotypes (Bogdan et al., 2018; Choi et al., 2020a). Studies also varied considerably in sample size (i.e., from N = 488 to N = 332,050 participants) and in the size of discovery GWAS used to construct PGSs, both of which impact the ability to detect significant associations (Bogdan et al., 2018). Indeed, both PTSD- and MDD-PGSs showed significant associations with general psychopathology in preadolescents when constructed from well-powered GWASs and no association when constructed from GWASs with considerably smaller sample sizes. Greater consistency in the associations observed across studies will likely emerge from the use of larger sample sizes and PGSs constructed from more powered GWASs.

The included studies also varied considerably in terms of approaches to the measurement and analysis of biological variables, which may partially explain some of the heterogeneity in results across the included studies. In the genomics literature, associations with a given PGS were found to vary between studies that did and did not control for the effects of other PGSs. For example, ADHD-PGSs were negatively associated with internalising in two studies of ABCD participants that controlled for general and specific symptom dimensions but not other PGSs (Waszczuk et al., 2021; Lahey et al., 2022). However, another study of the same sample found no evidence of association when controlling for other PGSs (Pat et al., 2022). In addition, some PGSs were not associated with a given symptom dimension when examined in isolation but showed significant positive associations when controlling for other PGSs. The clearest example of this was found for the relationship between depression-PGSs and internalizing, externalizing, somatic and detachment dimensions in ABCD participants (Waszczuk et al., 2021; Pat et al., 2022). These results highlight the importance of carefully considering the inclusion of other PGSs (even if not directly important to a given analysis) when examining polygenetic associations with transdiagnostic symptom dimensions. Not controlling for other PGSs can introduce confounding effects associated with genetic influences not accounted for in the analysis, which may explain differences in the results observed across studies. However, SNPs can also overlap substantially between

different PGSs, meaning that the inclusion of multiple PGSs in a single model can introduce multicollinearity among predictors (Choi et al., 2020b). Multicollinearity among predictors can produce unstable coefficient estimates, difficulties interpreting the individual contributions of a given predictor, and may also result in different observations regarding the significance and magnitude of associations across studies (P. Vatcheva and Lee, 2016).

4.5.3. Neuroimaging methods

In the neuroimaging literature, controlling for global effects (e.g., total GMV) resulted in substantially different findings. As mentioned, regionally-specific associations between symptom dimensions and numerous measures of brain structure (including both gray matter structure and white matter microstructure) tended to be largely or entirely non-significant after controlling for global effects. This coupled with consistent evidence that transdiagnostic symptom dimensions are associated with global measures of brain structure suggests that the neural architecture underlying broad expressions of psychopathology is widely distributed throughout the brain. This pattern of results calls into question the findings of several included studies, which reported regionally-specific associations found via whole-brain or ROI-based analyses not controlling for global effects. More broadly, it has important implications for research investigating the neurobiological underpinnings of psychopathology, which has historically focused on identifying disorder-specific correlates within relatively discrete brain regions. This is not to say that regionally-specific associations cannot be found (or that global associations are not driven by alterations within specific brain regions); (Hettwer et al., 2022) however, it does point to the importance of including global effects as a covariate in future analyses. Indeed, identifying regional associations with general and specific symptom dimensions that consistently survive controlling for global effects (e.g., lower pontine FA, cerebellar GMV) may serve as particularly important biological markers.

Another important consideration is the directionality of associations between biology and psychopathology. Measures of brain structure and function are often investigated for the potential as predictive markers of psychopathology; however, research indicates that psychopathology can also precede neurobiological abnormalities (Blok et al., 2023). Disentangling the temporal ordering of associations between biology and psychopathology is therefore critical to accurately modelling the structure and biological underpinnings of mental illness and to developing effective predictive models. Few of the included studies examined longitudinal associations between brain structure or function and transdiagnostic symptom dimensions. One study found that baseline measures of brain structure (i.e., SA and GMV) in the ABCD cohort predicted general and specific symptom dimensions across the first three waves of data collection (Romer et al., 2023). Conversely, another found that general psychopathology (derived from psychiatric assessment data across the lifespan) was associated with greater brain age at midlife (age 45) (Caspi et al., 2020). These findings likely indicate bi-directional effects between brain structure and psychopathology; however, further longitudinal research is urgently needed to better characterise these relationships.

4.6. Directions for future research

The review identified several directions for future research. Firstly, future research should directly investigate whether different biological correlates emerge for a given symptom dimension depending on the latent variable approach used in the analysis. Studies attempting to identify dimension-specific associations should control for the effects of other symptom dimensions (including general and specific transdiagnostic phenotypes). Bi-factor models may be particularly useful as they allow for identifying correlates that are associated with variance in psychopathology that is not shared across general and specific symptom dimensions; however, caution is needed when interpreting associations with phenotypes derived from this approach and efforts should be made to replicate associations with a given phenotype using different structural models. In terms of biological approaches, studies aiming to identify associations between symptom dimensions and PGSs should simultaneously model multiple PGSs where possible and ensure that correlations among PGSs are appropriately controlled for. Future research may also benefit from GWASs that specifically target transdiagnostic phenotypes (e.g., internalizing, externalizing) rather than disorder-specific phenotypes. Likewise, studies aiming to identify regional associations between symptom dimensions and brain structural correlates should control for global effects. Neuroimaging studies should also explore the contribution of specific brain regions (e.g., frontal and temporal regions) or networks (e.g., the DMN and DAN) to observed global associations. The review also identified several understudied symptom dimensions (e.g., thought disorder, somatic, detachment dimensions) and biological measures (e.g., task-based neural activation, white matter structure) that may yield further insights into the biological correlates of higher-order dimensions of psychopathology. Finally, longitudinal research across different (narrowly defined) developmental periods and age groups (particularly older adulthood) is urgently needed to inform our understanding of relationships between biological factors and transdiagnostic dimensions of psychopathology across the lifespan.

4.7. Limitations

There are several limitations to the review that are important to discuss. Firstly, there were notable methodological differences between the included studies (e.g., latent variable models, size of discovery and test samples, PGS construction and other measurement of biological variables, covariates included in analyses), which likely accounts for much of the heterogeneity observed in the results. Secondly, several associations were investigated in only one or few studies, preventing the ability to draw meaningful conclusions for these exposure/outcome relationships. Thirdly, only studies of general population samples were eligible for inclusion. Whilst this increases the generalisability of results, it is possible that biological variables will show different patterns of association at greater levels of symptom severity (e.g., in clinical samples). Fourth, although the review was intended to synthesise evidence from research investigating the biological correlates of transdiagnostic symptom dimensions *across the lifespan*, the vast majority of included studies (particularly within the neuroimaging literature) were limited to cross-sectional samples of youth and young adults. As such, we were unable to draw strong conclusions about age- and developmentally-specific biological associations across different symptom dimensions. Fifth, several limitations may influence the generalisability of findings from the review. For instance, a substantial number of the included studies were conducted using ABCD data and findings may not replicate across different samples of the same age group. More broadly, the majority of reviewed studies are based on Western samples, further adding to the issue of generalisability. This was particularly problematic in the genomics literature, where analyses were often explicitly restricted to samples of European ancestry. This is due to the fact that PGSs are primarily constructed from GWASs of European samples and tend to perform poorly when applied to samples of other ancestries, (Martin et al., 2019) suggesting that polygenetic associations with general and specific symptom dimensions may not replicate across different racial and ethnic groups. Sixth, the review only included studies examining higher-order symptom dimensions and subdimensions. The inclusion of studies investigating specific individual symptoms, signs, or maladaptive traits that are shared across diagnostic categories was beyond the scope of the current study; however, there will likely be important biological associations at these lower-levels of the symptom hierarchy. Finally, the findings of this review are presented via narrative synthesis rather than meta-analysis. This was due to vast methodological differences across studies and the limited number of associations between a given symptom dimension and biological variable that were examined

across multiple studies.

4.8. Conclusions

To our knowledge, this is the first systematic review to synthesize evidence from studies investigating the latent structure and underlying biology of psychopathology in the general population and to characterize these relationships across the lifespan. The findings of this review suggest that general psychopathology reflects broad genetic and neurobiological vulnerabilities that are shared across different manifestations of mental illness. The review found limited evidence of biological correlates that are uniquely associated with specific/lower-order transdiagnostic dimensions (e.g., internalizing, externalizing); however, this is likely due to substantial methodological differences and limitations between the existing studies. Several factors must be carefully considered when interpreting the results of studies investigating biological associations with general and specific transdiagnostic dimensions. This includes the choice of latent variable model (e.g., bifactor v. higher-order models), as well as the inclusion of biological controls (e.g., different PGSs, global measures of brain structure) and phenotypic covariates (e.g., controlling for general and specific symptom dimensions) in analyses. Several promising avenues for future research and important gaps in the current evidence base were identified. In particular, there is a need for more longitudinal research across different age groups and developmental periods in order to determine when and how biological differences impact the trajectories of general and specific/lower-order symptom dimensions.

Declarations of Interest

None.

Funding

NH was funded by a Research Training Program PhD scholarship provided by the Australian Government. No sponsor was involved in the design, collection, analysis, or interpretation of data, nor in the writing of the report or decision to submit this article for publication.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used Open AI in order to edit/refine text included in the main manuscript. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2023.105431.

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