Traces of psychopathology in the developing brain

Using brain covariance to disentangle similarities and differences between mental disorders in childhood and adolescence

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1. General summary

Empirical investigation into the structure of psychopathology supports a dimensional conceptualisation of what constitutes mental disorders over the classic categorical approach that is the current psychiatric nosology (Caspi et al., 2014; Kotov et al., 2017). In parallel, investigation into neurobiological mechanisms of psychopathology find robust evidence that brain patterns are shared across mental disorder diagnoses (Goodkind et al., 2015; Opel et al., 2020; Sha et al., 2019). Moreover, most mental disorders onset in the first three decades of life (Kessler et al., 2007), a time associated with large-scale reorganisation and maturation of the brain (Paus et al., 2008). Capitalising on these observations, it seems reasonable to assume that in order to understand psychopathology and what causes it, we must first understand what is shared and what is distinct across different forms of psychopathology.

In this thesis, we aimed to disentangle neurobiological correlates of different forms of psychopathology. We used multivariate statistics to investigate brain-behaviour associations related to dimensional and categorical measures of psychopathology. Specifically, given the important context of development, we performed this work in a sample of children and adolescents between the age of 5 and 21. Most of the participants of this sample had at least one mental disorder diagnosis. We then performed out-of-sample validation of our findings in three different samples of children and adolescent from the general population.

The main findings of this thesis will be integrated and discussed in the context of what is shared and what is distinct across different forms of psychopathology. In paper I, we investigated shared associations across measures of brain structure based on magnetic resonance imaging and measures of mental health, cognitive, and socio-environmental factors. We found evidence for two latent dimensions or "modes": one reflecting physical and cognitive maturation, and another reflecting a cross-diagnostic pattern linking social and cognitive troubles with reduced white matter surface area. Of note, these patterns were consistent across diagnostic groups. In paper II, we narrowed the focus down to the investigation of shared associations across measures of brain function and mental health measures only. Specifically, we utilised both categorical and dimensional approaches to psychopathology to identify their shared associations with functional magnetic resonance imaging resting-state functional connectivity. We found evidence for a shared pattern relating functional connectivity to five dimensions of psychopathology, recapitulating the psychopathology hierarchy. Autism-spectrum disorder was the only diagnostic category to

exhibit a specific brain functional connectivity pattern. In addition, we identified a connectivity pattern related to a categorical cross-diagnostic case-control pattern (i.e., no diagnosis versus all diagnoses) and a dimensional cross-diagnostic case-control pattern (i.e., allowing the diagnoses to cluster by their covariance with functional connectivity resulted in this pattern). To further expand on this relationship between brain measures and measures of psychopathology, we then investigated in paper III whether the categorical patterns identified in paper II were sensitive to questionnaires measuring psychopathology in yet another independent Norwegian cohort. Here, we found that the categorical connectivity patterns replicated, but that they were not sensitive to symptom load in the validation sample.

The findings of this thesis should be interpreted within the constraints of the chosen methodology. Notably, the data that forms the basis of the work is cross-sectional, thereby limiting any inferences to be made regarding change or developmental trajectory. Moreover, although out-of-sample validation was performed, generalisability of the findings was only partly demonstrated. Other considerations pertain to known limitations of functional brain imaging methodology, multivariate statistics, and studying developmental and clinical samples.

In sum, this thesis highlights the utility of multivariate statistics in disentangling brain-psychopathology relationships, as well as bridging the relevance of such associations from population-based studies to a clinical developmental sample. Importantly, the results suggest that the overarching associations are shared across diagnostic boundaries. Future studies may attempt to validate these shared brain-behaviour patterns across more comparable samples. The findings of this thesis support the notion that shared, transdiagnostic dimensions are more plausible operationalisations of psychopathology than categorical diagnoses. Although this has wide applications for the psychiatric nosology and the conceptualisation of psychopathology, an important caveat is that the design and methodology of this thesis do not permit inferences regarding aetiology or mechanistic insight. Towards achieving this goal, however, this thesis provides evidence that similarities show proclivity over differences in brain-behaviour associations relevant for a wide range of psychopathology in youth.

2. List of papers

I. Voldsbekk, I., Kjelkenes, R., Wolfers, T., Dahl, A., Lund, M. J., Kaufmann, T., Fernandez-Cabello, S., de Lange, A. G., Tamnes, C. K., Andreassen, O. A., Westlye, L. T., & Alnæs, D. (2023). Shared pattern of impaired social communication and cognitive ability in the youth brain across diagnostic boundaries. *Developmental Cognitive Neuroscience*, *60*, 101219. https://doi.org/10.1016/j.dcn.2023.101219

II. Voldsbekk, I., Kjelkenes, R., Dahl, A., Holm, M. C., Lund, M. J., Kaufmann, T., Tamnes, C. K., Andreassen, O. A., Westlye, L. T., & Alnæs, D. (2023). Delineating disorder-general and disorder-specific dimensions of psychopathology from functional brain networks in a developmental clinical sample. *Developmental Cognitive Neuroscience*, 101271. https://doi.org/10.1016/j.dcn.2023.101271

III. Voldsbekk, I., Kjelkenes, R., Frogner, E. F., Westlye, L. T., & Alnæs, D. (2023). Testing the sensitivity of diagnosis-derived patterns in functional brain networks to symptom burden in a Norwegian youth sample. *medRxiv*. https://doi.org/10.1101/2023.10.09.23296736 (submitted)

3. Abbreviations

DSM-5	Diagnostic and Statistical Manual of Mental Disorders – Fifth edition
ICD-11	International Classification of Diseases
RDoC	Research Domain Criteria
HiTOP	Hierarchical Taxonomy of Psychopathology
ADHD	Attention-deficit hyperactivity disorder
ASD	Autism-spectrum disorder
OCD	Obsessive-compulsive disorder
PFC	Prefrontal cortex
MRI	Magnetic resonance imaging
PNC	Philadelphia Neurodevelopmental Cohort
ABCD	Adolescence Brain Cognitive Development
BOLD	Blood-oxygen-level-dependant
DMN	Default mode network
DA	Dorsal attention
VA	Ventral attention
HBN	Healthy Brain Network
Brainmint	Brains and Minds in Transition
IRB	Institutional Review Board
REC	Regional Committee for Medical and Health Research Ethics
CBCL	Child Behaviour Checklist
SDQ	Strength and Difficulties Questionnaire
PCA	Principal component analysis
CCA	Canonical correlation analysis
ICA	Independent component analysis
PLS	Partial least squares
LV	Latent variable

4. Introduction

Since the beginning of time, humanity has been captivated by the mind and its mysteries. Despite centuries of investigation, and countless theories, however, we still know little of what causes a healthy mind to become a disordered mind. With the advent of brain imaging in humans, neuroscience has been searching for markers of disease, i.e., biomarkers, in the brains of individuals diagnosed with mental disorders. Beyond discovery of mental disorder mechanisms and causes, a big motivation to use brain imaging this way has been to improve diagnostics, and by extension, treatment of mental disorders (Insel et al., 2010). For example, by comparing the brains of healthy or non-diagnosed individuals (i.e., healthy controls) with individuals diagnosed with depression, studies have attempted to find biomarkers of the "depressed brain" (Winter et al., 2022). However, these biomarkers have remained elusive (Carvalho et al., 2020). Decades of research has yielded few consistent results regarding the difference between the depressed brain versus the healthy brain, and so forth. Instead, the accumulated research points to something else. Namely that compared to healthy controls, the most robust identified differences in brain structure (Goodkind et al., 2015; Opel et al., 2020) and brain function (Elliott et al., 2018; McTeague et al., 2017; McTeague et al., 2020; Sha et al., 2019) in individuals diagnosed with any type of mental disorder, such as anxiety, depression, and psychosis, seem to be shared across disorders.

These observations motivated the belief that in order to understand the structure of psychopathology and what causes it, we must first understand what is shared and what is unique across different mental disorders. For example, a common factor across mental disorders is that they typically first manifest during the first three decades of life (Kessler et al., 2007; Solmi et al., 2022), alluding to the importance of developmental context. This thesis represents novel contributions to the investigation of this landscape, with the overarching aim to improve our understanding of brain-based differences and similarities across mental disorders in childhood and adolescence. In the following section, relevant literature pertaining to the concepts of psychopathology, development, and brain imaging will be introduced.

4.1. Approaches to conceptualising psychopathology

The foundation of our current understanding of psychopathology is the modern diagnostic nosology, outlined in diagnostic manuals such as the Diagnostic and Statistical Manual of

Mental Disorders – Fifth Edition (DSM-5) (Association, 2013) and International Classification of Diseases (ICD-11) (Organization, 1992). Here, mental disorders are understood as discrete categories, for example defined in DSM-5 as "*a syndrome characterised by clinically significant disturbance in an individual's cognition, emotion regulation, or behaviour that reflects a dysfunction in the psychological, biological, or developmental processes underlying mental functioning*". An important element in this definition is the emphasis on clinically significant disturbance. This marks the boundary of each diagnostic category. Based on this boundary, you either have the disorder or not. This is classified based on meeting given criteria.

The primary purpose of a diagnostic nosology is to aid the clinician in treatment of mental disorders. A diagnosis will guide treatment selection, prognosis, and communication with patients and their families (First et al., 2015). Moreover, it represents the gold standard in separating "healthy" from "disordered", which has important implications for regulatory agencies, policy decisions, access to benefits, and other legal matters. Therefore, an important goal when developing the current diagnostic manuals was to improve the reliability of diagnosis classification by taxonomizing diagnostic criteria (Hyman, 2007).

Building on the biomedical framework (Deacon, 2013), the modern diagnostic nosology posits that mental disorders carve nature at its joints and represent "natural kinds" (Kendler, 2016). Implications of this is that each disorder has its own specific mechanisms and causes, akin to the way chickenpox is caused by a virus in somatic medicine. However, specific disease mechanisms for mental disorders remain largely unknown (Hyman, 2007). Instead, diagnostic criteria in the modern diagnostic nosology were developed based on clinical observation and represent descriptions of symptoms (Hyman, 2007).

What constitutes a symptom may vary, but usually implies disruptions of emotional, behavioural, or cognitive functioning, such as feelings of sadness, or inability to concentrate. The symptoms are typically measured in severity and duration and a diagnosis is given when a sufficient number of symptom criteria are met. As such, the diagnostic manuals imply that diagnoses represent something qualitatively different from one another, which by the use of diagnostic criteria, can be reliably dissected by different observers (Hyman, 2007). For example, to meet the diagnostic criteria for depression, there is a requirement in DSM-5 of at least four symptoms being present for the past two weeks, such as persistent sadness, loss of interest or pleasure, and low energy. To set a diagnosis, the clinician is expected to be able to disentangle these symptoms from symptoms of other possible diagnoses, such as anxiety, providing the patient with the most appropriate diagnosis given the symptom presentation.

In the everyday setting within the mental health services this often proves impossible, as patients rarely present a clinical picture that fits with the discrete descriptions of reality that the diagnostic criteria afford, alluding to the low validity of diagnoses (Kendell, 1989). Instead, mental disorders exhibit a high rate of comorbidity (Hasin & Kilcoyne, 2012) and heterogeneity (Fried & Nesse, 2015). Patients often present symptoms that align with more than one diagnosis, as symptoms often overlap across diagnoses (Forbes et al., 2023). As a result, patients often get diagnosed with multiple diagnoses, what is called comorbidity. In addition, two patients with the same diagnosis may present very different symptom profiles, profiles that may not even overlap, as symptoms belonging to the same diagnosis may vary a great deal. These observations may reflect that different diagnoses, although currently categorised as being separate things, actually have the same causes. Or, it could be that one diagnosis may have several possible causes culminating in partly overlapping symptom clusters, i.e., subgroups of diagnoses. Of course, these two possibilities are not mutually exclusive and can be true at the same time. Thus, although the diagnostic nosology has greatly improved mental disorder classification, with important applications in clinical practice, it is being increasingly recognised that it also comes with limitations, not least that it impedes the scientific discovery of pathophysiological markers of psychopathology (Hyman, 2007, 2021; Saggar & Uddin, 2019).

In response to this, initiatives have been made to refine the diagnostic nosology, such as the Research Domain Criteria (RDoC) (Insel et al., 2010) and Hierarchical Taxonomy of Psychopathology (HiTOP) (Kotov et al., 2017). RDoC was initiated by the National Institute of Mental Health in the US with the aim to identify new ways to classify mental disorders based on dimensions of observable behaviour and neurobiological measures. In order words, to encourage research into the pathophysiological mechanisms of mental disorders by a particular emphasis on genetic and neuroscientific research. The framework conceptualises dimensions of psychopathology as disruptions to one or more of six major domains of functioning: negative valence, positive valence, cognitive systems, social systems, arousal/modulatory systems, and sensorimotor systems. This way, RDoC encourages translational and integrative analysis, as well as new ways of grouping participants beyond the traditional case-control design. Of note, the RDoC understands mental disorders as dysfunction of fundamental, behavioural functions and their associated neural circuitry. As such, this framework aims to improve the aetiological understanding and classification of mental disorders by increased emphasis on biologically based research.

The HiTOP system for characterising psychopathology is developed based on covariation among diagnoses and symptoms and posits that psychopathology can be understood as a dimensional, hierarchical structure. This view is based on data-driven investigations into the latent structure of psychopathology, which suggest that a dimensional, hierarchical organisation represent a better fit (Caspi et al., 2014; Kotov et al., 2017; Lahey et al., 2012). This approach was inspired by the seminal observation that a single common factor, the p-factor, was the best model to explain the structure of psychopathology using confirmatory factor analysis (Caspi et al., 2014). Typically, the psychopathology hierarchy consist of this higher-order general factor, reflecting a general vulnerability to all psychopathology, followed by increasingly narrow dimensions of symptom clusters (Caspi et al., 2020). In HiTOP, the hierarchy consists of one broad "superspectrum" – i.e., the p-factor, followed by six, narrower "spectra": somatoform, internalising, thought disorder, detachment, disinhibited externalising, and antagonistic externalising (Kotov et al., 2017). In short, these spectra reflect symptoms of somatic complaints, anxiety or depression, psychosis or cognitive disorganisation, social withdrawal, impulsivity, and aggression, respectively. These spectra are then followed by increasingly narrow sub-spectra, until reaching the level of individual symptoms. Although this approach has many applications and advantages, HiTOP does not really offer any deeper conceptualisation of psychopathology beyond a description of its structure.

One advantage of dimensional conceptualisations of psychopathology is that comorbidity and heterogeneity of mental disorders are accounted for, by accommodating comorbidity and minimising heterogeneity. Another advantage of the hierarchical structure is that it facilitates investigation into neurobiological mechanisms of psychopathology at different levels, ranging from shared, transdiagnostic correlates to correlates of specific symptoms. This has great potential for the discovery of biomarkers and neurobiological mechanisms underlying psychopathology. However, although any such discovery may yield increased insight into neurobiological correlates of psychopathology, this does not automatically translate into mechanistic or aetiological insight (Saggar & Uddin, 2019). In turn, the implications for how to understand what psychopathology really is remains to be clarified. Nevertheless, a critical step towards achieving this aim is the understanding of what is shared and what is unique across different forms of psychopathology.

4.2. Neurodevelopment and its role in psychopathology

Throughout childhood, adolescence and early adulthood, the brain undergoes some of the most dramatic changes of the entire lifespan. Supporting an expanding repertoire of motor, cognitive and social skills required for adulthood and independence from caregivers, major alterations occur in both brain structure (Mills et al., 2016) and function (Paus et al., 2008; Power et al., 2010). Briefly, alterations in brain structure implicate an inverted U-shaped trajectory for grey matter, while white matter exhibit an extended increase as one approach adulthood (Giedd et al., 2015; Tamnes et al., 2017). This process seems to develop in a posterior-anterior manner, aligned with the functional partition of the cortex along a sensory-association axis (Walhovd et al., 2014).

Developmental trajectories of brain function and functional networks are not as well mapped, but recent work suggest that the maturation of functional networks follow the same posterior-anterior sensory-association axis of development (Edde et al., 2021; Sydnor et al., 2021). Sensory and motor functions and their implicated regions develop during early childhood, while higher-order cognitive functions and implicated transmodal functional networks seem to be later maturing and still developing throughout adolescence. Brain regions assumed to underlie these later-developing networks involve the association cortices and fronto-parietal regions of the brain.

The developmental perspective and the role of developmental context in psychopathology has been called out as a critical dimension missing from early research into neurobiological mechanisms (Kaczkurkin et al., 2020) as well as the original RDoC framework (Casey et al., 2014; Conradt et al., 2021; Durbin et al., 2022). The reasoning here is that understanding typical development is a pre-requisite to understanding what goes “awry” in psychopathology. This developmental framework is essential also because it may shed light on whether any detected neurobiological or other differences between patients and controls are the result of developmental delay, deviation, or regression, which has wide implications for prevention and treatment (Casey et al., 2014).

Accumulating behavioural, cognitive, neural, and genetic evidence support a neurodevelopmental origin of mental illness (Buckholtz & Meyer-Lindenberg, 2012; Insel, 2010; Paus et al., 2008; Uhlhaas et al., 2023). Specifically, this hypothesis entails that aberrant neurodevelopmental processes occurring during early life, likely due to a combination of genetic and environmental factors, sets an individual on a path of increased risk for developing mental disorders. As mentioned, most mental disorders emerge during youth, with some emerging even during early childhood (Kessler et al., 2007). This includes

classic neurodevelopmental disorders such as attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD), but also conditions such as anxiety and obsessive-compulsive disorder (OCD). Conditions typically developing later, in adolescence and early adulthood, such as mood disorders and schizophrenia, also show signs of a neurodevelopmental origin, such as delayed developmental milestones in the first year and implicated genes being involved in brain development (Insel, 2010). Understanding the role of the neurodevelopmental context in the development of mental illness is therefore of pivotal importance.

One framework to explain the co-occurrence of mental disorder onset with brain maturation is the framework of "sensitive periods" (Blakemore & Mills, 2014; Fuhrmann et al., 2015; Knudsen, 2004; Reh et al., 2020). Sensitive periods refer to time-limited developmental windows in which environmental exposures have marked effects on the function and structure of the brain due to increased plasticity. This idea was originally introduced by the observation that sensory deprivation in early life can impede successful development of vision circuitry in the brain (Hooks & Chen, 2007). The increased plasticity of the brain during childhood and adolescence as part of neurodevelopment affords adjustment and maturation but may come at the cost of increased risk for mental illness when combined with genetic and environmental vulnerability (Fuhrmann et al., 2015). A similar framework is the concept of developmental cascades, which posits that transactions at different timescales (e.g., perinatal, infancy, adolescence), constructs (cognition, mood, behaviour) and levels (molecular, individual, social) can have a cumulative cascading effect on subsequent development (Masten & Cicchetti, 2010).

If psychopathology is the result of cumulative risk leaving traces in the developing brain, this was wide implications both for our understanding of psychopathology, and for prevention and treatment. Research into the neurobiological correlates of psychopathology during development thus represents two avenues in which neuroimaging research can aid psychopathology understanding (Nielsen et al., 2020). First, grounded in the biomedical framework of mental disorders, this research may yield additional insight into disease mechanisms relevant for individual predictions and personalised treatment (Saggar & Uddin, 2019). Second, grounded in the developmental framework, this research may yield additional insight into neurodevelopment and which factors are involved in psychological risk and resilience more broadly, either protecting or exposing an individual to progressing from vulnerability to "disease" (Fuhrmann et al., 2015; Lehman et al., 2017). In the pursuit of

psychopathology aetiology, understanding mechanisms of neurodevelopment and how they relate to shared and distinct forms of psychopathology becomes important.

4.3. Risk factors

Although the precise aetiology of psychopathology remains largely unknown, attempts have been made to identify specific factors linked to increased risk. For schizophrenia, such investigations have identified factors such as genetic variants, drug use, obstetric complications, prenatal infections, urbanicity, migration, lower educational performance, brain pathology, and childhood adversity (Murray et al., 2017). In addition, a common theme is that non-specific symptom manifestations in childhood are linked to later psychopathology (Arslan et al., 2021; Lahey et al., 2016). Of note, general psychopathology in adulthood has been linked to lower cognitive function and compromised brain integrity years prior to symptom onset (Caspi et al., 2014), alluding to cognition and brain development as important early indicators or risk factors for later psychopathology. In line with the developmental framework, higher-order cognitive functions such as working memory and executive functioning are some of the last cognitive abilities to mature, corresponding to later development of implicated brain regions and circuits (Larsen & Luna, 2018). For example, these higher-order cognitive functions are believed to recruit circuitry involving the prefrontal cortex, a brain region consistently found to be impaired in mental disorders (Chini & Hanganu-Opatz, 2021). However, no one factor, or one group of factors, alone, have been found to be causal. Rather, psychopathology appears to result from a hugely complex combination of these and probably many other factors, consistent with the developmental cascades framework. In this thesis, we therefore employed a wider, multivariate investigation of associations between mental health data and other factors to illuminate relevant patterns for further investigation.

4.4. Neuroimaging as a method to study the brain in psychopathology

Magnetic resonance imaging (MRI) is a non-invasive imaging technique that has revolutionised the study of the human brain. Both physical states and mental states have been attempted quantified using this methodology, with various biological properties to form the basis of the investigation. Briefly, MRI works by inducing a strong magnetic field and then identifying separate types of biological tissue by quantifying the degree of magnetisation, which differs across different types of tissue (Weishaupt et al., 2006). In this thesis, two major and widely used approaches of MRI have been used, namely structural and functional

MRI. More detail regarding these methodologies and their application in the study of psychopathology is outlined below.

4.4.1. Structural MRI

Structural MRI or structural imaging refer to MRI sequences that aim to delineate the anatomical structure of the brain based on its different types of tissue. Typically, this MRI image is obtained using a T_1-weighted sequence, which involves using imaging parameters that optimise separation of grey matter and white matter, in which the former appears grey, and the latter appears white (Bischoff-Grethe & Fennema-Notestine, 2023). These images are then often reconstructed and segmented using automated pipelines, such as from FreeSurfer (Fischl, 2012), a software toolbox which affords quantification of specific brain structures, such as by their thickness, volume, and surface area, measures which can then be compared and monitored across time and across populations.

Abnormalities in brain structure has been linked to both dimensional and categorical approaches to psychopathology, with substantial overlap in neural correlates across diagnostic boundaries in adult patients (Goodkind et al., 2015; Hettwer et al., 2022; Opel et al., 2020). In a population-based sample of youth called the Philadelphia Neurodevelopmental Cohort (PNC) (Satterthwaite et al., 2016), overall psychopathology has been linked to brain white matter aberrations across classical diagnostic boundaries (Alnaes et al., 2018), as well as reduced grey matter volume (Kaczkurkin et al., 2019; Moberget et al., 2019). Reduced grey matter volume was also found linked to overall psychopathology in children aged 9-10 from the Adolescent Brain Cognitive Development study (ABCD) (Casey et al., 2018) (Durham et al., 2021; Mewton et al., 2022; Romer et al., 2023) and prefrontal areas in children aged 6-10 (Snyder et al., 2017). Importantly, general psychopathology correlated with greater negative deviations in normative cortical development (Parkes et al., 2021) but brain structure measures could not predict within-person change in symptom burden across time (Romer et al., 2023).

4.4.2. Functional MRI

Functional MRI or functional imaging refer to MRI sequences that aim to infer something about the “function” of the brain, i.e., brain activity. This is achieved by following the rationale that a net increase of oxygenated to deoxygenated blood implies increased brain activity, as neural transmission is very energy consuming (Raichle, 1987). As such, functional

MRI involves imaging the level of deoxyhemoglobin, specifically the blood-oxygen-level-dependant (BOLD) response across regions of the brain over time (Kim & Ogawa, 2012). If imaged during rest, i.e., when doing nothing other than lying still inside the scanner bore, this approach is referred to as resting-state functional MRI (Biswal et al., 1995). This data can then be separated into "networks" of intrinsic brain activation across brain regions based on their covariation. This network approach is often called functional connectivity or the functional connectome (Biswal et al., 2010). The rationale of this approach is that brain regions that covary, talk together or are "more connected." This can be defined as brain activity showing coherent temporal fluctuations across spatial networks that are present when an individual is not partaking in higher cognitive tasks (Moreno-Ayure et al 2020). These intrinsic networks of the brain can be estimated in different ways, with one common approach resulting in the following seven networks (Yeo et al., 2011): the default mode network (DMN), the visual network, the somatomotor network, the fronto-parietal/control network, the salience/ventral attention network, the limbic network, and the dorsal attention (DA) network. As their names imply, these networks are involved in different functional circuits typically fluctuating at rest.

As with brain structure, investigations into the overlap across diagnostic categories in adults suggest shared neural correlates of brain function (McTeague et al., 2017; McTeague et al., 2020; Sha et al., 2019). Using diagnostic data in ABCD, a hierarchical model of psychopathology consisting of a general factor and three lower order factors (externalising, internalising and thought disorder), was associated with common and dissociable patterns of functional connectivity (Lees et al., 2021). Specifically, common patterns involved hypoconnectivity within the DA and retrosplenial-temporal networks, hyperconnectivity between the frontoparietal and ventral attention (VA) networks, and between the DA network and amygdala. In addition, the externalising factor was uniquely associated with hyperconnectivity between the salience and VA networks, while internalizing was characterized by hypoconnectivity between the DMN and cingulo-opercular networks.

Likewise, recent efforts have established specific patterns of connectivity across dimensions derived from symptom data. Also in the ABCD sample, robust associations were found between connectivity and a general psychopathology factor, as well as a neurodevelopmental factor (Karcher et al., 2021). The general factor was associated with hypoconnectivity within the DMN, an association that was evident, and stronger, in the neurodevelopmental factor. In addition, the neurodevelopmental factor was characterised by associations with the cingulo-opercular, DA and "other" networks.

Connectivity patterns in ABCD were also used to predict the p-factor (Hong et al., 2023) and sub-domains of psychopathology (Chen et al., 2022). Across dimensions of psychopathology, several studies consistently report a shared association with reduced functional segregation of the control or executive network from other core networks (Chen et al., 2022; Elliott et al., 2018; Lees et al., 2021), as well as reduced connectivity within the DMN (Chen et al., 2022; Karcher et al., 2021).

In addition, delayed maturation of functional connectivity networks seems to be a common transdiagnostic correlate (Vanes & Dolan, 2021). For example, children and adolescents with subclinical symptoms of mental illness in the PNC sample showed diverging developmental trajectories of their brain functional connectivity, compared to healthy controls (Kaufmann et al., 2017).

4.4.3. Multivariate brain-behaviour associations

A promising approach to further understand the factors relating brain development to psychopathology is the utilisation of multivariate statistics. Multivariate statistics affords mapping of relevant associations across many measurements at once, accommodating correlations between individual measures and yielding increased statistical power to detect latent structures in the data if they exist (McIntosh & Lobaugh, 2004; Wang et al., 2020). This way, clusters of relevant factors can be identified, for example, the similarities and differences in brains of individuals with different forms of psychopathology.

Multivariate approaches in adults have revealed a positive-negative population dimension linking brain functional connectivity with lifestyle, demographic, and psychometric measures (Smith et al., 2015), thereby characterising an intricate web of relevant factors across domains. This “positive-negative” axis of covariation has been replicated in adolescents (Modabbernia, Reichenberg, et al., 2021) and children aged 9-10 from ABCD (Alnæs et al., 2020; Modabbernia, Janiri, et al., 2021), highlighting the existence of these patterns already early in life. In paper I of this thesis, we use a similar approach to investigate latent patterns linking brain development and clinical, cognitive, and socio-environmental factors in children diagnosed with mental disorders.

Other lines of investigation have used multivariate statistics to derive dimensions of psychopathology based on covariance in brain data. For example, a partly replicable pattern of both shared and unique aspects of anxiety, irritability, and ADHD were related to distributed functional connectivity in two clinical samples of mainly children (Linke et al.,

2021). Another recent study identified four neuroimaging patterns related to phenotypic variation across children with and without an ADHD diagnosis (Ball et al., 2018). In PNC, symptom dimensions were derived by finding their maximal correlation with functional connectivity (Xia et al., 2018). Dimensions of mood, psychosis, fear, and externalisation symptoms exhibited both unique patterns of connectivity, as well as a shared pattern of abnormal within-network connectivity of the DMN and frontoparietal network. In addition, they shared reduced segregation between the DMN and executive (fronto-parietal and salience) networks.

Using a similar multivariate approach in ABCD (Kebets et al., 2023), brain covariance across both functional and structural data revealed overlapping symptom dimensions as those reported previously using symptom data alone (Michelini et al., 2019). Multivariate approaches also support the general psychopathology association with reduced cortical volume in youth (Bashford-Largo et al., 2023) and children from ABCD (Durham et al., 2023). Together, these findings strongly support the utility of the dimensional conceptualisation of psychopathology in the pursuit of neurobiological mechanisms of mental disorders. However, the similarities and differences across different forms of psychopathology need also be mapped out in clinical samples. In paper II of this thesis, we use multivariate methods to investigate this question.

4.5. Replicability and generalisability

One of the challenges for traditional case-control research into neurobiological correlates of specific mental disorders is the lack of replicability and generalisability across studies and across populations of patients (Uddin et al., 2017). Indeed, the neuroimaging field as a whole has had this problem to varying degrees (Botvinik-Nezer & Wager, 2022). Replicability refers to the ability to obtain similar results as previous research when using new data or methodology (Jadavji et al., 2023). A non-negligible part of this problem is likely due to methodological issues, such as small sample sizes or overfitting in large samples (Botvinik-Nezer & Wager, 2022; Davatzikos, 2019; Poldrack et al., 2020; Varoquaux, 2018). However, the categorical approach to psychopathology may also have hampered this pursuit (Hyman, 2007; Saggar & Uddin, 2019). For research to be clinically relevant, and one day be able to identify reliable biomarkers of psychopathology, establishing generalisability represents a critical prerequisite (Poldrack et al., 2020; Woo et al., 2017). In all three papers of this thesis, we tested the generalisability of our findings to an independent cohort.

4.6. Summary

A major target for clinical neuroscience is establishing robust neurobiological correlates of psychopathology. This is important to better understand the mechanisms underlying psychopathology, which in turn may yield insight into psychopathology aetiology, which then may improve the diagnostic nosology, and thereby improve prevention and treatment. In response to the limitations of a categorical approach to diagnosis, novel approaches to conceptualising psychopathology have been developed (Caspi et al., 2014; Insel et al., 2010; Kotov et al., 2017). There is hope and accumulating evidence that these dimensional, transdiagnostic approaches will yield improved detection of relevant neurobiological mechanisms. Another important perspective to consider in this pursuit is the developmental context of psychopathology.

In this thesis, we investigate multivariate brain-behaviour associations in a clinical developmental sample and relate these to different operationalisations of psychopathology (i.e., dimensional vs categorical). We establish that dimensional, transdiagnostic approaches to psychopathology map onto patterns of covariance in both brain structure, brain function, and cognitive and socio-environmental factors, while categorical approaches are less successful. Finally, we attempt to validate our results in three different independent cohorts.

5. Main research objectives and hypotheses

The overarching aim of this thesis was to use multivariate statistics and brain-based models to increase our understanding of what is shared and what is unique across different forms of psychopathology. Additionally, we aimed to test the extent to which these associations generalise to other populations.

These aims were operationalised through specific objectives, which were each addressed in the following empirical papers:

5.1. Paper 1

The objective of this study was to establish reliable brain-behaviour associations across brain structure and clinical, cognitive, and socio-environmental factors in a developmental clinical sample. Secondly, to investigate whether these associations look similar or different across different categories of psychopathology. And thirdly, to validate these results in an independent cohort. Based on the p-factor framework and other dimensional conceptualisations of psychopathology, we expected these brain-behaviour associations to reveal transdiagnostic patterns across brain structure and clinical-cognitive-socio-environmental factors.

5.2. Paper 2

The objective of this study was to contrast categorical and dimensional approaches to psychopathology in terms of their covariance with resting-state functional connectivity. Secondly, to validate these results in an independent cohort. Again, we expected these associations to show that brain covariance aligns better with dimensional approaches to psychopathology.

5.3. Paper 3

The objective of this study was to test the generalisability of brain associations of categorical approaches to psychopathology in an independent Norwegian cohort. Given the trouble with replicating previous functional connectivity findings, we expected low degree of replicability and generalisability.

6. Methodology

6.1. Samples

This thesis include data from three publicly available datasets, in addition to locally collected data. Table 1 shows an overview of the samples. For paper I, data from the Healthy Brain Network (HBN) (Alexander et al., 2017) and PNC (Satterthwaite et al., 2016) were included. For paper II, data from HBN and the ABCD cohort (Casey et al., 2018) were included. For paper III, data from HBN and the Norwegian Brains and Minds in Transition (Brainmint) sample were included.

	Paper I	Paper II	Paper III
Cohort	HBN / PNC	HBN / ABCD	HBN / Brainmint
Sample size	1732 / 1253	2109 / 3504	1666 / 531
Types of measures	Structural MRI, behavioural, clinical, cognitive, socio-environmental	Resting-state functional MRI, clinical	Resting-state functional MRI, clinical
Age (mean ± SD)	10.52 ± 3.17 / 15.26 ± 3.54	10.99 ± 3.16 / 9.94 ± 0.62	10.91 ± 3.14 / 17.69 ± 2.83
Age range	5-21 / 8-21	5-21 / 9-10	5-21 / 9-25

Table 1. Overview of the samples used in this thesis. HBN; Healthy brain network. PNC; Philadelphia neurodevelopmental cohort. ABCD; Adolescent brain cognitive development cohort. MRI; magnetic resonance imaging. SD; standard deviation.

HBN sample. HBN is a clinically enriched developmental sample from four different sites across New York City, USA. The project is led by the Child Mind Institute with the aim to understand the heterogeneity of developmental psychopathology. The data collection is still ongoing. Participants included thus far ranged from 5 to 21 years old and most of them met the criteria for at least one neurodevelopmental or mental disorder diagnosis. They were recruited through "community-referred recruitment", meaning that families with concerns regarding the mental health of their child were encouraged to participate. The participants underwent a range of examinations, including physical and cognitive testing, psychological assessment, diagnostic screening, MRI, electroencephalography, and genetics. The only

exclusion criteria for participation were the presence of any acute safety concerns, severe behavioural or cognitive impairment (e.g., being nonverbal), or medical concerns that would likely confound brain-related findings. HBN was approved by the Chesapeake Institutional Review Board (IRB) (https://www. chesapeakeirb.com/).

PNC sample. PNC is a population-based sample from the greater Philadelphia area, USA. The project aimed to understand the link between genetics, behaviour, and the brain during development. Participants were 8 to 21 years old and were recruited after visiting a primary care facility associated with the Children's hospital of Philadelphia. As a result, youth with a range of medical conditions were included, from well-child visits to more severe medical problems. Participants underwent MRI, cognitive tests, psychological assessment, and genetic testing. A formal psychiatric assessment of diagnosis was not performed. Inclusion criteria for participation were ability to give informed consent (parental consent was required for individuals <18 years old), English proficiency, and ability to participate in computerised assessments such as cognitive tests. PNC was approved by The University of Pennsylvania and Children's hospital of Philadelphia IRB.

ABCD sample. ABCD is a population-based sample recruited from 21 sites across all over USA. The study is still ongoing and plans to follow >10,000 children for ten years with extensive assessments and multiple timepoints. The aim is to conduct a longitudinal study of brain development and child health in a socio-demographically representative cohort. Participants were recruited for the baseline timepoint at age 9-10, which is the data included in this thesis. Ethical review and approval of the protocol was obtained from the IRB at the University of California, San Diego, as well as from local IRB (Auchter et al., 2018).

Brainmint sample. Brainmint is a convenience-based sample of youth recruited from the Oslo region in Norway. This study is also ongoing, with the aim to understand the role played by brain plasticity in the increased risk for mental illness during adolescence. Participants included thus far range from 9 to 25 years old and were recruited through social media or due to participation in collaborating studies. The participants underwent MRI, cognitive tests, and psychological assessment. Brainmint was approved by the Regional Committee for Medical and Health Research Ethics (REC), South-East division in Norway.

6.2. Behavioural measures

HBN sample. Behavioural data from HBN used in this thesis include clinical, cognitive, and socio-environmental factors. In paper I, all available behavioural data in HBN was

initially included, prior to data cleaning and dimensionality reduction. In paper II and paper III, mental health symptom scores obtained from the parent-reported Child Behaviour Checklist (CBCL) (Achenbach & Rescorla, 2001) and Strength and Difficulties Questionnaire (SDQ) (Goodman, 1997) were used, respectively. We used both the raw symptom item scores and the summary scores for each subscale. For CBCL, these subscales were: Anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behaviour, and aggressive behaviour. SDQ subscales included emotional problems, conduct problems, hyperactivity, peer problems, and prosocial behaviour. In paper II, we also used diagnostic information obtained from a computerised interview (KSADS) (Kaufman et al., 1997). We then categorised diagnoses as either "ADHD", "ASD", "anxiety disorders", "mood disorders", "other neurodevelopmental disorders", "other disorders" or "no diagnosis".

PNC sample. Behavioural data from PNC used in this thesis include cognitive measures and clinical measures (paper I). In PNC, cognitive abilities were assessed using a computerised test battery of 12 tests, measuring executive function, working memory, episodic memory, verbal and non-verbal reasoning, and social cognition (Gur et al., 2014). We included a general cognitive ability factor, computed as the first principal component of a principal component analysis (PCA) run on these test results, which was derived by an earlier study (Alnaes et al., 2018). In addition, we included a social cognitive score, which was computed as the sum of the two social cognition tests: the Penn Emotion Identification Test and Penn Emotion Differentiation Test (Moore et al., 2015). Finally, we included a normative deviation score for cognitive abilities, which was estimated using normative modelling on the cognitive test data, also derived by an earlier study (Kjelkenes et al., 2022). This measure is an estimation of the degree of deviation from a normative age trajectory, i.e., the relative cognitive development compared to same-aged peers. Clinical measures in PNC included 129 symptom scores obtained with a computerised clinical interview (GOASSESS) (Calkins et al., 2015). Based on earlier work, these symptom scores were decomposed into 7 clinical components using independent component analysis (ICA): Attention/ADHD, anxiety, conduct disorder, depression, psychosis prodrome, mania, and obsessive-compulsive disorder (Alnaes et al., 2018). In addition, we included a general symptom burden measure (mean clinical ICA-score).

ABCD sample. Behavioural data from ABCD used in this thesis include mental health symptom scores obtained from parent-report CBCL. In paper II, we used both the raw symptom item scores and the summary scores for each subscale.

Brainmint sample. Behavioural data from Brainmint used in this thesis include mental health symptom scores obtained from self-report SDQ. In paper III, we used the raw symptom item scores to compute summary scores for each subscale.

6.3. Brain MRI measures

Full details regarding the MRI acquisition and pre-processing steps are given in each respective paper. A short description is provided below.

HBN sample. Brain data from HBN used in this thesis include structural MRI (paper I) and resting-state functional MRI (paper II and III). HBN MRI data was collected at four sites with different scanners and slightly different acquisition parameters. Structural MRI was obtained from one of four different T_1-weighted sequences, selecting the sequence with the best estimated quality per individual. Pre-processing steps included the recon-all segmentation pipeline of FreeSurfer (Fischl, 2012). Quality control steps was done using MRIQC (Esteban et al., 2017). Resting-state functional MRI was obtained as the first fMRI sequence out of four, in which the latter two included naturalistic movie viewing. Pre-processing steps included motion correction, high-pass filtering, smoothing, distortion correction, registration, ICA-AROMA and FIX, all run using the FMRIB Software Library (FSL) (Smith et al., 2004). Again, quality control steps was done using MRIQC (Esteban et al., 2017). The resting-state timeseries were then parcellated into 100 parcels using the Schaefer parcellation (Schaefer et al., 2018). Finally, the functional connectivity matrix was estimated by running network analysis on the parcels using partial correlations in FSLNets.

PNC sample. Brain MRI data from PNC used in this thesis include structural MRI (paper I). In PNC, structural MRI was obtained with a T_1-weighted sequence acquired on a single 3T Siemens (TrioTim) scanner. Pre-processing steps included the same steps as for HBN data described above.

ABCD sample. Brain data from ABCD used in this thesis include resting-state functional MRI (paper II). Pre-processing and network analysis of this data was done by another study (Kebets et al., 2023).

Brainmint sample. Brain data from Brainmint used in this thesis include resting-state functional MRI (paper III). Resting-state functional MRI was obtained using a T2*-weighted sequence on a 3T GE SIGNA Premier scanner. Pre-processing and quality control steps included fMRIPrep (Esteban et al., 2019) and MRIQC (Esteban et al., 2017). Parcellation and network analysis steps were then the same as for HBN data described above.

6.4. Statistical analysis

The backbone of this thesis is the use of multivariate statistics to understand the complex relatedness of brain-behaviour associations. The main statistical analyses were carried out in MATLAB R2020b (MathWorks, 2020). Supplementary analyses and plotting were carried out in R version 4.1.2 (R Team, 2018). In paper I, we used an integrated approach consisting of canonical correlation analysis (CCA) and independent component analysis (ICA) (Miller et al., 2016). In paper II, we used partial least squares (PLS) to compare rotated versus non-rotated/contrast-based latent patterns (Krishnan et al., 2011). In all three papers, we investigated the generalisability of findings using out-of-sample validation. Below these methodological approaches will be outlined in some more detail.

6.4.1. CCA-ICA

CCA estimates orthogonal canonical variates or modes of covariation, reflecting maximal correlation across two matrices. These modes represent linear combinations of one matrix that explain variance in linear combinations of the other matrix across participants. In paper I, we used this methodology to investigate brain-behaviour associations across structural MRI and clinical, cognitive, and socio-environmental variables. To aid interpretability of the modes, we submitted the outputted CCA scores to ICA. This involved finding independent components drawn across both brain and behaviour variables. To ensure stability and robustness of the detected modes, permutation tests were run. Moreover, data was submitted to PCA prior to CCA-ICA analysis and reliability of this decomposition was assessed using split-half reliability.

6.4.2. PLS

PLS estimates latent variables (LV) reflecting maximal covariance across two matrices. Briefly, this involves an estimation of a cross-covariance matrix, which is then inputted to singular value decomposition for dimensionality reduction. To estimate PLS models using data measured on different scales, all brain MRI and behavioural measures where normalised prior to estimating PLS. The weights of each input variable onto each LV say something about which variables are relevant for this pattern, akin to factor loadings. To ensure stability and robustness of the detected LVs, permutation testing and bootstrapping with replacement were included as intermediate steps. In paper II, we used PLS to investigate shared

associations across functional connectivity and mental health data (symptoms and diagnostic categories).

6.4.3. Out-of-sample validation

Given that multivariate statistics is prone to overfitting (Poldrack et al., 2020), a final step to ensure robustness of results is the use of out-of-sample validation. In this thesis, out-of-sample-validation was performed in all three papers. In paper I, the brain-behaviour associations detected across structural MRI and clinical, cognitive, and socio-environmental variables were validated in an independent cohort with slightly different clinical and cognitive variables. In paper II, the shared associations detected between functional connectivity and symptom data were validated in both an independent sample from HBN and an independent cohort with overlapping variables. In paper III, the shared associations detected between functional connectivity and diagnostic categories were validated in an independent cohort and used to predict symptom scores across samples. Joint across these validation efforts, the validation was performed on the MRI variables as the initial step. MRI variables in the validation sample were decomposed using weights derived in the original sample. Validation was then performed as the correlation across the MRI variables of the original sample and the derived MRI variables of the validation sample. Permutation testing was used to test significance. As a second step, generalisability was assessed by testing whether the derived MRI variables of the validation sample could predict behavioural measures in the validation sample. The reliability of these associations was assessed using bootstrapping with replacement.

6.5. Ethical considerations

Ethical considerations form an essential aspect of research. For the work conducted as part of this thesis, particular focus was put on ethical conduct in data collection when participants are children and adolescents. In addition, considerations were made with respect to the ethical implications of this research for those studied (i.e., children and adolescents) and for society at large.

For the three publicly available datasets, we were not part of the teams that collected the data. As such, we did not have any direct contact with any of the participants or otherwise any influence over how this data collection was carried out. However, all three studies had procedures for data collection and handling in line with their IRB approval.

For the Brainmint sample, we were responsible for the data collection and handling of data. The study was conducted in line with the Declaration of Helsinki and has been reviewed and approved by the REC (2019/943), South-East division in Norway. All participants provided written informed consent prior to their participation in the study, and this was given after being provided with information regarding all aspects of participation. Particularly, this included information regarding what participation entails in terms of tasks and how we will ensure confidentiality of their data. Participants were also informed that they could withdraw their consent to participate at any time, without any consequence, and that they could ask to have their data deleted. This information was provided both via verbal communication and in written information sheets. For participants under the age of 16, both parents/legal guardians provided written informed consent on their behalf.

Given that many participants were under the age of 18, we took particular care to ensure that participation felt safe and easy. MRI is considered safe, but lying still in a small space for a long time can feel tiresome, especially for children and adolescents. During the MRI scan, the scanning personnel would check with the participant at regular intervals if they felt ok to proceed, or otherwise end the exam prematurely. Parents were also allowed to join their child inside the scanner room if the child needed them close.

As an additional safety measure, all MRI scans were examined by a qualified neuroradiologist to detect any incidental findings in the brain of the participants. For any clinically relevant findings, procedures were in place to follow these up in the regular hospital system.

To ensure safe handling and storage of data, both from Brainmint and from the publicly available samples, all data was stored and analysed on the University of Oslo secure server for storage of sensitive data (TSD; https://www.uio.no/english/services/it/research/sensitive-data/). Data handling procedures that ensure privacy/GDPR has been approved by the Norwegian Agency for Shared Services in Education and Research (https://sikt.no/en/home).

Children and adolescents represent a vulnerable population, particularly youth with elevated symptoms of psychopathology. Conducting research in this group comes with an ethical responsibility for how such research is later communicated and used, for example in the media or in policy making. Research should be transparent, and the chosen research questions should feel relevant and beneficial to those being studied. Currently, the biological underpinnings of mental disorders and their developmental context remains largely unknown. Communication of such associations should therefore be cautious. Only later, when building on work such as this thesis, benefits for the individual patient or youth may be within reach.

Translating and replicating findings across research cohorts and populations represents a critical step towards this aim, and this thesis represents one step on this path. Advances in machine learning and predictive modelling comes with great potential. However, it is essential that models and their findings are not based on, and exasperating, bias in data, leading to stigma and unfair predictions. The utility of being able to predict the onset of mental disorders and preventative interventions must be balanced with the possibility of causing harm through potential discrimination and stigmatisation for those being labelled as at-risk. In the advent of personalised medicine, this issue must be overcome in order for any replicated findings to be useful.

7. Summary of papers

7.1. Paper 1: Shared pattern of impaired social communication and cognitive ability in the youth brain across diagnostic boundaries

Background. Abnormalities in brain structure are shared across diagnostic categories. Given the high rate of comorbidity, the interplay of relevant behavioural factors may also cross these classic boundaries.

Methods. We aimed to detect brain-based dimensions of behavioural factors using CCA and ICA in a clinical youth sample (n=1732, 64% male, age: 5-21 years).

Results. We identified two correlated patterns of brain structure and behavioural factors. The first mode reflected physical and cognitive maturation r=.92, p=.005). The second mode reflected lower cognitive ability, poorer social skills, and psychological difficulties (r=.92, p=.006). Elevated scores on the second mode were a common feature across all diagnostic boundaries and linked to the number of comorbid diagnoses independently of age. Critically, this brain pattern predicted normative cognitive deviations in an independent population-based sample (n=1253, 54% female, age: 8-21 years), supporting the generalisability and external validity of the reported brain-behaviour relationships.

Conclusion. These results reveal dimensions of brain-behaviour associations across diagnostic boundaries, highlighting potent disorder-general patterns as the most prominent. In addition to providing biologically informed patterns of relevant behavioural factors for mental illness, this contributes to a growing body of evidence in favour of transdiagnostic approaches to prevention and intervention.

7.2. Paper 2: Delineating disorder-general and disorder-specific dimensions of psychopathology from functional brain networks in a developmental clinical sample

Background. The interplay between functional brain network maturation and psychopathology during development remains elusive. To establish the structure of psychopathology and its neurobiological mechanisms, mapping of both shared and unique functional connectivity patterns across developmental clinical populations is needed.

Methods. We investigated shared associations between resting-state functional connectivity and psychopathology in children and adolescents aged 5-21 (n=1689). Specifically, we used PLS to identify LVs between connectivity and both symptom scores and diagnostic information. We also investigated associations between connectivity and each diagnosis specifically, controlling for other diagnosis categories.

Results. PLS identified five significant LVs between connectivity and symptoms, mapping onto the psychopathology hierarchy. The first LV resembled a general psychopathology factor, followed by dimensions of internalising- externalising, neurodevelopment, somatic complaints, and thought problems. Another PLS with diagnostic data revealed one significant LV, resembling a cross-diagnostic case-control pattern. The diagnosis-specific PLS identified a unique connectivity pattern ASD. All LVs were associated with distinct patterns of functional connectivity. These dimensions largely replicated in an independent sample (n=420) from the same dataset, as well as to an independent cohort (n = 3504).

Conclusion. This suggests that covariance in developmental functional brain networks supports transdiagnostic dimensions of psychopathology.

7.3. Paper 3: Testing the sensitivity of diagnosis-derived patterns in functional brain networks to symptom burden in a Norwegian youth sample

Background. Aberrant brain network development represents a putative key aetiological component in mental disorders, which typically emerge during childhood and adolescence. Previous resting-state functional MRI studies have identified brain connectivity patterns reflecting psychopathology, but the generalisability to other samples and politico-cultural contexts has not been established.

Methods. We investigated whether a previously identified cross-diagnostic case-control and ASD-specific pattern of resting state functional connectivity (discovery sample; children and adolescents aged 5-21 from New York City, USA; n = 1666) would replicate in a Norwegian convenience-based sample of youth (validation sample; children and adolescents aged 9-25 from Oslo, Norway; n = 531). As a test of generalisability, we investigated if these diagnosis-derived resting-state functional connectivity patterns were sensitive to levels of symptom burden in both samples, based on an independent measure of symptom burden (i.e., not diagnostic criteria).

Results. Both the cross-diagnostic and ASD-specific functional connectivity pattern was replicated across samples. Connectivity patterns were significantly associated with thematically appropriate symptom dimensions in the discovery sample. In the validation sample, the ASD-specific functional connectivity pattern showed a weak, inverse relationship with symptoms of conduct problems, hyperactivity, and prosociality, while the cross-diagnostic pattern was not significantly linked to symptoms.

Conclusion. Diagnosis-derived connectivity patterns in a developmental clinical US sample are replicable in a convenience sample of Norwegian youth, however, they were not predictive of mental health symptoms.

8. Discussion

By mapping the associations across brain and mental health measures using multivariate statistics, this thesis aimed to disentangle what is shared and what is unique across different forms of psychopathology. This investigation utilised different brain measures and different measures of mental health, including also cognitive and socio-environmental factors, along with out-of-sample validation of each finding. The results that arose from this investigation support the utility of transdiagnostic approaches to psychopathology, consistently showing proclivity for shared, dimensional patterns over categorical, diagnosis-specific patterns. In the following section, the main findings and their implications will be discussed.

8.1. Main findings

In paper I, we investigated shared associations across measures of brain structure and measures of mental health, cognitive, and socio-environmental factors. We found evidence for two latent dimensions or "modes": one reflecting physical and cognitive maturation, and another reflecting a cross-diagnostic pattern linking social and cognitive troubles with reduced white matter surface area. Of note, these patterns were consistent across diagnostic groups. There was no evidence for any unique or differentially related latent patterns for specific diagnostic groups. These findings suggest that in terms of overarching brain to clinical-cognitive-socio-environmental patterns in children and adolescents, these are shared across different diagnostic groups. Importantly, the association linking brain structure and lower cognitive ability were validated in an independent cohort.

Given that brain-behaviour patterns across diagnostic groups seemed to be shared, we wanted to dig a little deeper into this relationship. In paper II, we therefore narrowed the focus down to the investigation of shared associations across measures of brain function and mental health measures only. Specifically, we utilised both categorical and dimensional approaches to psychopathology to identify their shared associations with resting-state functional connectivity. We found evidence for a shared pattern relating functional connectivity to five dimensions of psychopathology, recapitulating the psychopathology hierarchy. ASD was the only diagnostic category to exhibit a specific connectivity pattern. In addition, we identified a connectivity pattern related to a categorical cross-diagnostic case-control pattern (i.e., no diagnosis versus all diagnoses) and a dimensional cross-diagnostic case-control pattern (i.e., allowing the diagnoses to cluster by their covariance with functional

connectivity resulted in this pattern). The symptom dimensions were replicated in an independent cohort, but their associated connectivity pattern was not.

To further expand on this relationship between brain measures and measures of psychopathology, we then investigated in paper III whether the categorical patterns identified in paper II were sensitive to measures of psychopathology in yet another independent cohort. Here, we found that the categorical diagnosis-derived connectivity patterns replicated, but that they were not sensitive to symptom load in the validation sample.

From these findings two major themes arise, namely that 1) brain patterns seem to be shared across different forms of psychopathology, and 2) that dimensional approaches to psychopathology capture more variance in brain measures than do categorical approaches.

8.2. Brain-behaviour associations are shared

Different diagnoses, if they indeed reflect "natural kinds" each with their own specific disease mechanisms and causes, would be expected to yield differential patterns related to risk or vulnerability. In this context, patterns of brain development and maturation would be expected to relate to each diagnosis in specific ways. For example, if a specific form of deviation from expected brain maturation was associated with depression or risk for developing depression, we would expect to detect this brain-behaviour association as a latent dimension in our multivariate analyses. And similarly, if vulnerability to psychopathology is instead cross-diagnostic and shared (as postulated by the HiTOP and p-factor framework), we would expect to detect shared latent dimensions of brain-behaviour associations.

One major advantage of multivariate statistics is the ability to jointly model complex relationships across measures that may or may not be independent. In the context of both the brain and psychopathology, this advantage is crucial, given that both brain measures and psychopathology measures are related to each other. Concurrently, both brain measures and psychopathology are related to many other factors, representing risk factors, protective factors, confounding factors, and so on. In the disentanglement of this complex interplay, multivariate statistics as a methodological approach really shine, and can provide insight into the above question of shared versus specific latent dimensions across diagnoses.

Paper I provides a step towards untangling these relationships in the context of diagnoses, investigating similarities and differences in these relationships across different diagnostic categories in children and adolescents. Perhaps not so surprisingly, individuals with and without mental disorder diagnoses are more alike than they are different in terms of

their overarching brain-behaviour associations. Important developmental domains such as physical maturation, cognitive ability, and social skills exhibit shared associations with brain structure across all individuals. However, beyond this latent pattern, we also found another latent pattern, relating brain structure to cognition and social skills. And this pattern was more pronounced in diagnosed individuals as compared to individuals with no diagnoses, as shown in figure 1. Of note, this pattern was shared across all diagnostic categories. No diagnostic group stood out to be driving this finding.

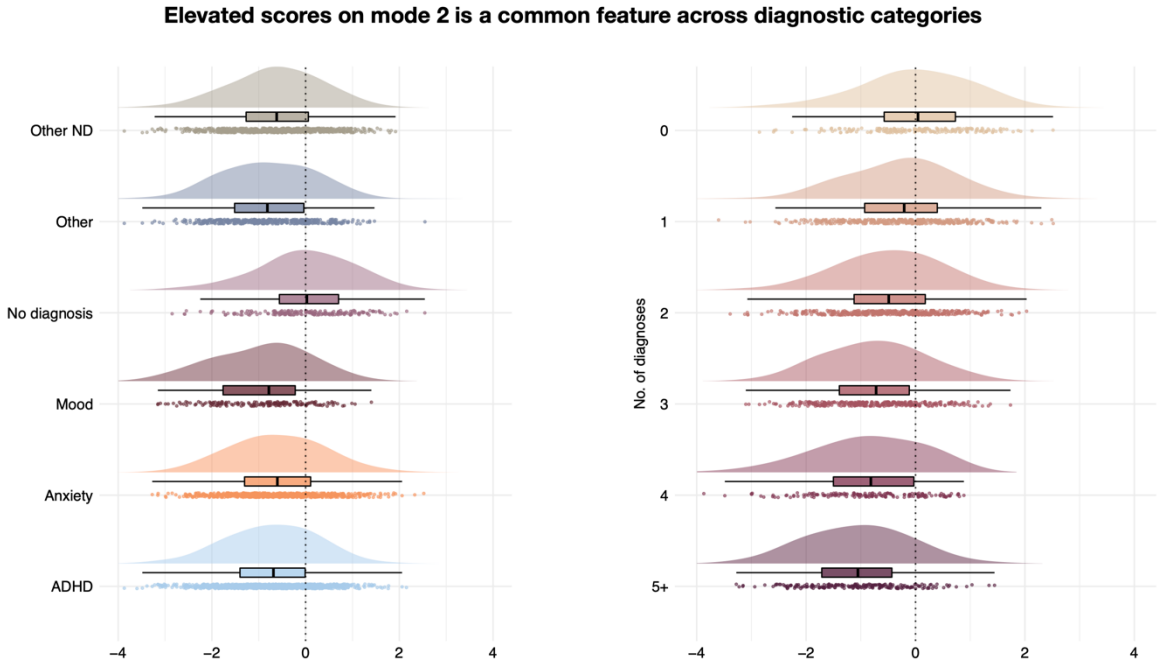

Figure 1. Loadings on mode 2 across diagnostic categories in paper I.

This fits with an increasing number of previous studies showing a "positive-negative" axis linking brain features to clinical, cognitive, social, and environmental factors in both adulthood (Smith et al., 2015), adolescence (Modabbernia, Reichenberg, et al., 2021), and childhood (Alnæs et al., 2020; Modabbernia, Janiri, et al., 2021; Xiao et al., 2023). Of note, the work of paper I was able to extend this "positive-negative" axis found in population-based samples to a clinical developmental sample. This demonstrates the relevance of this "positive-negative" axis also across diagnostic groups. This is compelling evidence in favour of shared mechanisms across mental disorders.

Shared mechanisms across mental disorders are also in line with previous literature finding risk factors of mental disorders to be non-specific and with low predictive utility of specific diagnoses (Lynch et al., 2021). Together, this literature does not support the

understanding of mental disorder diagnoses as “natural kinds,” at least not in terms of their specific underlying mechanisms separating one diagnosis from another. While we cannot infer any causality or aetiology based on shared associations and explained variance (Fried, 2020), the overwhelming coherence of this literature points to similarities rather than differences in brain-behaviour associations across diagnostic boundaries. This alludes to the specificity of diagnosis mechanisms being small and inconsequential, at best.

Narrowing the focus down to neurobiological correlates only, the question of similarities and differences across psychopathology was further tackled in paper II. Here, we investigated how covariance in functional connectivity would cluster in relation to dimensional and categorical measures of psychopathology. We found that across both approaches, the covariance with functional connectivity supported shared patterns. These shared patterns cut across both categorical (i.e., cross-diagnostic case-control) and dimensional boundaries, favouring a general psychopathology factor as the dimension explaining most covariance with functional connectivity. These findings fit with the increasingly coherent story of shared brain-behaviour patterns across diagnostic categories.

Neurobiological correlates of mental disorders in adults are increasingly found to be shared across diagnostic boundaries (Goodkind et al., 2015; Hettwer et al., 2022; McTeague et al., 2017; McTeague et al., 2020; Opel et al., 2020; Sha et al., 2019). For example, aberrations in the functional connectivity of the DMN, fronto-parietal network, and salience network were found to be shared across eight psychiatric disorders (Sha et al., 2019). Another shared dimension in adult patients link psychopathology to somatosensory-motor network dysconnectivity (Kebets et al., 2019). Interestingly, shared brain structural abnormalities in adults were found across diagnoses of major depression, bipolar disorder, schizophrenia, and OCD, while abnormalities in neurodevelopmental conditions such as ADHD and ASD were largely independent (Opel et al., 2020). In paper II, we found evidence supporting that the shared patterns detected in adults can be extended to diagnosed youth, and that the shared pattern also encompass neurodevelopmental disorders.

A shared pattern across diagnostic boundaries aligns with studies finding neurobiological correlates of a general psychopathology factor in youth (Chen et al., 2022; Durham et al., 2021; Elliott et al., 2018; Kaczkurkin et al., 2019; Karcher et al., 2021; Kebets et al., 2023; Lees et al., 2021; Mewton et al., 2022; Romer et al., 2020; Romer et al., 2018; Romer et al., 2021; Snyder et al., 2017; Xiao et al., 2023; Xie et al., 2023). This consistency is found across studies deriving a general psychopathology factor from both symptom measures and diagnostic information. However, most of these studies also find

neurobiological correlates of narrower symptom dimensions (Chen et al., 2022; Durham et al., 2021; Kaczkurkin et al., 2019; Karcher et al., 2021; Kebets et al., 2023; Lees et al., 2021; Mewton et al., 2022; Romer et al., 2020). In synchrony, paper II of this thesis found evidence for narrower latent symptom dimensions from the psychopathology hierarchy, in addition to diagnosis-specific patterns. There is also evidence for neurobiologically informed sub-types of diagnoses in youth (Kaczkurkin et al., 2020). These findings suggest that although much of the variance in brain measures are shared across different forms of psychopathology, there is also evidence supporting specificity.

If brain-behaviour associations were to inform the understanding of psychopathology, these findings support the move towards transdiagnostic, dimensional approaches. Although this work does not inform aetiology or delineate causal mechanisms of psychopathology, the findings of this thesis converge with previous research identifying shared, cross-diagnostic neurobiological correlates of psychopathology. An implication of this body of literature is that the time is ripe for the psychiatric nosology to embrace a fundamentally different approach to classification of mental disorders. In this approach, similarities across disorders should be accounted for. This is not to say that specificity does not exist or should be ruled out. A comprehensive nosology should be able to accommodate both.

8.3. Categorical vs dimensional approaches to psychopathology

The consistent report of shared patterns across different forms of psychopathology has implications for how we may understand the structure of psychopathology. Not least, it has implications for the utility of categorical versus dimensional approaches to conceptualising psychopathology. A strength of paper II was the investigation of brain-psychopathology covariance in a sample with a high degree of comorbidity and access to both symptom measures and diagnostic information. This allowed the investigation into how these two different approaches to psychopathology differ in their covariance with functional connectivity.

We found evidence that dimensional approaches to psychopathology capture more variance in functional connectivity than do categorical approaches. An important caveat in relation to this result is the difference between dimensional and categorical measures in terms of their statistical properties. Dimensional, continuous variables afford more covariance to be captured than do dichotomous, categorical variables by nature of their own inherent variance. The fact that dimensional measures of psychopathology exhibited more shared associations

with functional connectivity than categorical measures likely reflect this difference. That is not to say that this negates a superiority of dimensional measures over categorical measures. This statistical difference between the two represent a fundamental difference in the approach to psychopathology structure, as discussed in the introduction, which may or may not reflect the "nature" of psychopathology. The superiority of dimensional measures in capturing neurobiological correlates may reflect that this represents a "truer" classification of what psychopathology really is. Of course, this question goes beyond the scope of the results of this thesis, but nevertheless represent an interesting idea to be investigated further. A recent meta-analysis of taxometric research support the utility of dimensional approaches to psychopathology, finding that dimensional models outnumber those supporting taxonic (i.e., categorical) models five to one (Haslam et al., 2020).

As outlined in the above section, both dimensional and categorical approaches to psychopathology converged on shared neurobiological mechanisms. This can be interpreted as evidence favouring a dimensional approach. However, it can also be used to advocate the utility of categorical diagnoses. Indeed, the convergence on a shared factor across disorders from studies using both symptom dimensions, as well as dichotomous diagnosis information, supports the notion of a latent vulnerability factor on which the diagnostic categories represent extremes (Sprooten et al., 2022). Following from this, the categorical psychiatric nosology has not necessarily lost its relevance, even if it proves inferior in the detection of reliable neurobiological mechanisms. Instead, diagnostic categories may be improved and re-categorised based on incoming evidence, neurobiological and other (Insel et al., 2010). As outlined in the introduction, the utility of a psychiatric nosology goes beyond the one aim of detecting aetiological mechanisms. It serves other functions too, such as informing treatment and policy decisions. Transdiagnostic dimensional approaches may improve assessment reliability and inference validity compared to the current diagnostic system (Ruggero et al., 2019), with subsequent potential to tailor treatment and intervention. However, somewhere down the line, a binary decision must be made regarding treat or not to treat (Eaton et al., 2023). As diagnoses may represent extremes of psychopathology dimensions (Sprooten et al., 2022), their utility with respect to this cut-off remains a strong argument for their continued relevance.

With regards to clinical utility, paper II and paper III combined found evidence for limited degree of generalisability of functional connectivity patterns derived from both dimensional and categorical measures of psychopathology. In paper II, we replicated symptom dimensions of a latent pattern, while the connectivity dimensions did not. In paper

III, we attempted to replicate diagnosis-derived cross-diagnostic and ASD-specific functional connectivity patterns to a primarily healthy sample of youth. While the connectivity patterns themselves in fact replicated, they were not sensitive to symptom burden in the new sample, greatly diminishing their clinical utility. This lack of generalisability mirrors previous work finding functional connectivity results to be difficult to replicate (Marek et al., 2022; Nour et al., 2022; Uddin et al., 2017; Winter et al., 2022). Implications of this finding is that although dimensional approaches to psychopathology can account for many of the limitations faced by categorical approaches, their superior utility is not yet established, for example as foundations for biomarkers.

It is becoming increasingly recognised that perhaps it is not feasible to find biomarkers specific to each diagnosis if they are in fact not "natural kinds." Instead, biomarkers related to dimensions of psychopathology, with the general p-factor already spearheading this approach, may represent more feasible targets. This approach has already been embraced, with studies reporting, for example, ability to predict the p-factor based on functional connectivity in the ABCD sample (Hong et al., 2023). However, while this currently is a vibrant research field with many discoveries likely to be made in the near future, this research is faced by many of the same challenges as before (Marek et al., 2022). For any neurobiological correlate of psychopathology to have potential as a biomarker, it must show efficacy in both individual-level prediction and ability to generalise to new populations (Poldrack et al., 2020; Woo et al., 2017). Although some work show potential (Traut et al., 2022), reliable biomarkers have remained elusive (Carvalho et al., 2020). The implication of the consistent lack of generalisability of brain-behaviour associations is that much work remains in the pursuit of reliable psychopathology biomarkers, and before we can determine the utility of dimensional versus categorical approaches to psychopathology in relation to clinical relevance.

8.4. Developmental context

A final note on possible implications of this thesis concerns the developmental context of psychopathology. Although the focus of this thesis has not been trajectories of developmental change and how these relate to psychopathology, childhood and adolescence may represent sensitive periods in which the interplay between brain maturation and psychopathology is particularly susceptible. As such, understanding differences and similarities in the brains of children and adolescents, and how these in turn relate to psychopathology, represents a

crucial step towards understanding the role of brain maturation in psychopathology, with potential implications for both psychopathology aetiology, prevention, and treatment.

In paper I, we modelled age as part of the model. As expected, age was found to be an important source of covariance between brain measures and other measures in a sample consisting of children and adolescents between the age of 5 and 21. In fact, it was the variable with the highest loading onto mode 1. In turn, most of the variance related to age was captured in this first mode, leaving the cross-diagnostic latent pattern identified as mode 2 largely age-invariant. Similarly, we found that controlling for age or not did not significantly alter the shared associations between functional connectivity and psychopathology measures in paper II. As such, it seems that the associations between brain and psychopathology in this thesis were mostly independent of age. This goes against earlier work showing, for example, diverging neural correlates of ASD as a function of age (Uddin et al., 2013).

One interpretation of this finding is that the shared brain-socio-cognitive vulnerability across diagnostic groups does not reflect delayed maturation or any other maturational process, but rather a general vulnerability separating healthy individuals from diagnosed individuals irrespective of their age or developmental stage. This aligns with recent reports that prenatal and early life factors remain the most important factors for later brain health (Walhovd et al., 2023). However, it remains a very essential caveat that the research of this thesis is based on cross-sectional data, which does not permit any inferences to be made regarding developmental trajectories. As such, this interpretation remains speculative.

Cognition is consistently found to be an important associate of psychopathology across the lifespan. In adult clinical samples, lower reduced cognitive functioning separate patients from healthy controls (Abramovitch et al., 2021). In youth clinical samples, lower cognitive functioning is linked to higher overall psychopathology (Castellanos-Ryan et al., 2016). In paper I, lower cognitive ability showed a replicable association with brain structure across clinical groups and a population-based sample of youth. In line with this, several studies have found cognitive development to be a key risk factor for psychopathology (Caspi et al., 2020; Kjelkenes et al., 2022; Xiao et al., 2023). Indeed, other studies have found the association between brain structure and psychopathology to disappear when accounting for cognitive functioning (Mewton et al., 2022). To disentangle the role of brain maturation and developmental context in psychopathology, this work shows that cognition remains an essential piece of the puzzle.

8.5. Methodological considerations

As with any research study, the work that forms the basis of this thesis must be interpreted within the strengths and limitations of the chosen study design and methodology. In the following section, these methodological considerations will be discussed.

8.5.1. Samples

The commonality across all three papers of this thesis is the HBN sample. This sample consisted of children and adolescents, with the majority being under 15 years old (average age 11 years old) and diagnosed with at least one mental disorder. Although the sample was recruited from four different sites across New York City in order to increase diversity within the sample, the majority of the sample were white. This restricts the generalisability of findings to wider populations, especially outside a US context. In addition, families were encouraged to participate if they had any "concerns" regarding their child. Although this approach likely facilitated enrichment of psychiatric and neurodevelopmental conditions in the sample, this limits generalisability to other populations.

A strength of this thesis is that the results obtained in HBN were attempted validated in three independent cohorts. However, these three cohorts were all very different from HBN, in each their own way. First, the PNC sample were generally older, with a mean age around 15 years old. In addition, this sample was recruited from the general population and not enriched with mental disorders. Similarly, the ABCD sample is a population-based sample of children aged 9-10. Although this overlaps with the mean age of HBN, this limited age range strongly differs from that in HBN, in which the age range was from 5 to 21 years old. Finally, the Brainmint sample consisted of Norwegian youth that were both older (mean age around 17 years old) and again not enriched with mental disorders. These differences between the samples are likely to limit the degree that generalisation realistically can be performed.

In paper I, we could replicate the pattern relating brain-cognition in PNC, but not psychopathology. In ABCD in paper II, we could replicate symptom dimensions, but not connectivity patterns. In Brainmint in paper III, we could replicate diagnosis-derived connectivity patterns, but these were not sensitive to symptom load. Although challenges with generalisability is a common theme across the field (Marek et al., 2022), a limitation of the current thesis is that the obtained lack of generalisability may also reflect the differences inherent between samples.

8.5.2. Using fMRI in developmental samples

Conducting neuroimaging research in children and adolescents is a challenge due to increased rates of motion and other sources of noise in the data (Dosenbach et al., 2017). Conducting neuroimaging research in children that also have mental disorders is on yet another level. More than 50% of the HBN sample was diagnosed with ADHD. As expected, motion was a big issue in this data. Although we performed several additional steps to ameliorate the effects of such confounds, including motion correction steps and control checks of the influence of missing signal on the processing of the remaining data, this remains a limitation of this thesis.

8.5.3. Cross-sectional design

Given that all data included in this thesis was cross-sectional, we cannot make any inferences regarding development or maturation per se. As already mentioned, this represents a major caveat of this thesis. Other limitations of a cross-sectional design are the ability to detect systematic confounds erroneously attributed to age differences, and the ability to infer causality between variables. Of course, causality inference is neither easily achieved within a longitudinal design. The discussion of what is required to make causal inferences goes beyond the scope of this thesis.

That being said, cross-sectional designs also have some advantages. For example, the comparatively lower cost and time investment required to obtain cross-sectional data enables collection of larger samples. In turn, this yields increased statistical power and improved generalisability, as a larger portion of the underlying population has been sampled. In this thesis, we relied on relatively large samples of youth, with more than 1000 individuals in HBN. For one, this enabled us to utilise multivariate statistics to investigate our research questions.

8.5.4. Multivariate statistics

Although multivariate statistics have many strengths and overcome challenges in the field such as lack of independence between measures, this methodology also comes with some caveats. First, individual bivariate associations obtained within a multivariate analysis cannot be interpreted in isolation, but only in relation to the bigger picture of the overarching latent association. Second, multivariate methods such as CCA and PLS are prone to overfitting (Botvinik-Nezer & Wager, 2022). We performed several steps to secure robustness of our

results, including permutation testing, hold-out validation, and external validation. However, our results did only partly generalise across cohorts. As such, our results need further replication to rule out overfitting. Third, as mentioned above, to obtain reliable results using multivariate statistics, a fairly large sample size is required to have sufficient statistical power (Varoquaux, 2018). In paper I, we performed dimensionality reduction using PCA to overcome this limitation. Still, although the included samples of this thesis were relatively large, they were still in the lower range for this type of methodology, which may also have reduced the robustness of our results.

8.6. Concluding remarks

The main aim of this thesis was to disentangle similarities and differences across different forms of psychopathology during childhood and adolescence. All three papers included in this thesis applied multivariate statistics and out-of-sample validation in independent cohorts. We have investigated shared associations between brain structure and clinical-cognitive-social-environmental factors, as well as between brain functional networks and categorical and dimensional measures of psychopathology. In addition, we have contrasted these associations across diagnostic boundaries and tested their generalisability across samples. The work of this thesis shows the utility of multivariate statistics in disentangling brain-behaviour relationships, as well as bridging the relevance of such associations from population-based studies to a clinical developmental sample. Importantly, the results suggest that overarching brain-behaviour associations are shared across diagnostic boundaries, supporting transdiagnostic, dimensional approaches to psychopathology.

The utility of these findings towards clinical relevance should be further investigated. To achieve this, further replication and generalisation is required. Future studies may attempt to validate shared brain-behaviour patterns across more comparable samples. In addition, the utilisation of several MRI modalities in the same multivariate analysis may yield additional insight into neurobiological correlates of psychopathology. In terms of the structure of psychopathology, this thesis argues that shared, transdiagnostic dimensions are more plausible operationalisations of psychopathology than categorical diagnoses. Although this has wide applications for the psychiatric nosology and the conceptualisation of psychopathology, an important caveat is that the methodology of this thesis does not permit inferences to be made regarding aetiology or mechanistic insight. Towards achieving this

goal, however, this thesis provides evidence that similarities show proclivity over differences in brain-behaviour associations relevant for psychopathology in youth.

9. References

Abramovitch, A., Short, T., & Schweiger, A. (2021). The C Factor: Cognitive dysfunction as a transdiagnostic dimension in psychopathology. *Clinical Psychology Review*, *86*, 102007. https://doi.org/https://doi.org/10.1016/j.cpr.2021.102007

Achenbach, T. M., & Rescorla, L. A. (2001). Manual for the ASEBA school-age forms & profiles: an integrated system of multi-informant assessment Burlington, VT: University of Vermont. *Research Center for Children, Youth, & Families*, *1617*.

Alexander, L. M., Escalera, J., Ai, L., Andreotti, C., Febre, K., Mangone, A., Vega-Potler, N., Langer, N., Alexander, A., & Kovacs, M. (2017). An open resource for transdiagnostic research in pediatric mental health and learning disorders. *Scientific data*, *4*(1), 1-26.

Alnaes, D., Kaufmann, T., Doan, N. T., Cordova-Palomera, A., Wang, Y., Bettella, F., Moberget, T., Andreassen, O. A., & Westlye, L. T. (2018). Association of Heritable Cognitive Ability and Psychopathology With White Matter Properties in Children and Adolescents. *JAMA Psychiatry*, *75*(3), 287-295. https://doi.org/10.1001/jamapsychiatry.2017.4277

Alnæs, D., Kaufmann, T., Marquand, A. F., Smith, S. M., & Westlye, L. T. (2020). Patterns of sociocognitive stratification and perinatal risk in the child brain. *Proceedings of the National Academy of Sciences*, *117*(22), 12419-12427.

Arslan, İ. B., Lucassen, N., Van Lier, P. A., De Haan, A. D., & Prinzie, P. (2021). Early childhood internalizing problems, externalizing problems and their co-occurrence and (mal) adaptive functioning in emerging adulthood: a 16-year follow-up study. *Social psychiatry and psychiatric epidemiology*, *56*, 193-206.

Association, A. P. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5* (Vol. 5). American psychiatric association Washington, DC.

Auchter, A. M., Mejia, M. H., Heyser, C. J., Shilling, P. D., Jernigan, T. L., Brown, S. A., Tapert, S. F., & Dowling, G. J. (2018). A description of the ABCD organizational structure and communication framework. *Developmental Cognitive Neuroscience*, *32*, 8-15.

Ball, G., Malpas, C. B., Genc, S., Efron, D., Sciberras, E., Anderson, V., Nicholson, J. M., & Silk, T. J. (2018). Multimodal Structural Neuroimaging Markers of Brain Development and ADHD Symptoms. *American Journal of Psychiatry*, *176*(1), 57-66. https://doi.org/10.1176/appi.ajp.2018.18010034

Bashford-Largo, J., Nakua, H., Blair, R. J. R., Dominguez, A., Hatch, M., Blair, K. S., Dobbertin, M., Ameis, S., & Bajaj, S. (2023). A shared multivariate brain-behavior relationship in a transdiagnostic sample of adolescents. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*. https://doi.org/https://doi.org/10.1016/j.bpsc.2023.07.015

Bischoff-Grethe, A., & Fennema-Notestine, C. (2023). Structural magnetic resonance imaging. In *APA handbook of neuropsychology, Volume 2: Neuroscience and neuromethods, Vol. 2* (pp. 535-550). American Psychological Association. https://doi.org/10.1037/0000308-026

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

Biswal, B. B., Mennes, M., Zuo, X. N., Gohel, S., Kelly, C., Smith, S. M., Beckmann, C. F., Adelstein, J. S., Buckner, R. L., Colcombe, S., Dogonowski, A. M., Ernst, M., Fair, D., Hampson, M., Hoptman, M. J., Hyde, J. S., Kiviniemi, V. J., Kotter, R., Li, S. J., Lin, C. P., Lowe, M. J., Mackay, C., Madden, D. J., Madsen, K. H., Margulies, D. S., Mayberg, H. S., McMahon, K., Monk, C. S., Mostofsky, S. H., Nagel, B. J., Pekar, J. J., Peltier, S. J., Petersen, S. E., Riedl, V., Rombouts, S. A., Rypma, B., Schlaggar, B. L., Schmidt, S., Seidler, R. D., Siegle, G. J., Sorg, C., Teng, G. J., Veijola, J., Villringer, A., Walter, M., Wang, L., Weng, X. C., Whitfield-Gabrieli, S., Williamson, P., Windischberger, C., Zang, Y. F., Zhang, H. Y., Castellanos, F. X., & Milham, M. P. (2010). Toward discovery science of human brain function. *Proc Natl Acad Sci U S A*, *107*(10), 4734-4739. https://doi.org/10.1073/pnas.0911855107

Blakemore, S. J., & Mills, K. L. (2014). Is adolescence a sensitive period for sociocultural processing? *Annu Rev Psychol*, *65*, 187-207. https://doi.org/10.1146/annurev-psych-010213-115202

Botvinik-Nezer, R., & Wager, T. D. (2022). Reproducibility in Neuroimaging Analysis: Challenges and Solutions. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*. https://doi.org/https://doi.org/10.1016/j.bpsc.2022.12.006

Buckholtz, J. W., & Meyer-Lindenberg, A. (2012). Psychopathology and the human connectome: toward a transdiagnostic model of risk for mental illness. *Neuron*, *74*(6), 990-1004. https://doi.org/10.1016/j.neuron.2012.06.002

Calkins, M. E., Merikangas, K. R., Moore, T. M., Burstein, M., Behr, M. A., Satterthwaite, T. D., Ruparel, K., Wolf, D. H., Roalf, D. R., & Mentch, F. D. (2015). The Philadelphia Neurodevelopmental Cohort: constructing a deep phenotyping collaborative. *Journal of Child Psychology and Psychiatry*, *56*(12), 1356-1369.

Carvalho, A. F., Solmi, M., Sanches, M., Machado, M. O., Stubbs, B., Ajnakina, O., Sherman, C., Sun, Y. R., Liu, C. S., & Brunoni, A. R. (2020). Evidence-based umbrella review of 162 peripheral biomarkers for major mental disorders. *Translational Psychiatry*, *10*(1), 152.

Casey, B., Oliveri, M. E., & Insel, T. (2014). A neurodevelopmental perspective on the research domain criteria (RDoC) framework. *Biological Psychiatry*, *76*(5), 350-353.

Casey, B. J., Cannonier, T., Conley, M. I., Cohen, A. O., Barch, D. M., Heitzeg, M. M., Soules, M. E., Teslovich, T., Dellarco, D. V., & Garavan, H. (2018). The adolescent brain cognitive development (ABCD) study: imaging acquisition across 21 sites. *Developmental Cognitive Neuroscience*, *32*, 43-54.

Caspi, A., Houts, R. M., Ambler, A., Danese, A., Elliott, M. L., Hariri, A., Harrington, H., Hogan, S., Poulton, R., Ramrakha, S., Rasmussen, L. J. H., Reuben, A., Richmond-Rakerd, L., Sugden, K., Wertz, J., Williams, B. S., & Moffitt, T. E. (2020). Longitudinal Assessment of Mental Health Disorders and Comorbidities Across 4 Decades Among Participants in the Dunedin Birth Cohort Study. *JAMA network open*, *3*(4), e203221-e203221. https://doi.org/10.1001/jamanetworkopen.2020.3221

Caspi, A., Houts, R. M., Belsky, D. W., Goldman-Mellor, S. J., Harrington, H., Israel, S., Meier, M. H., Ramrakha, S., Shalev, I., Poulton, R., & Moffitt, T. E. (2014). The p Factor: One General Psychopathology Factor in the Structure of Psychiatric Disorders? *Clin Psychol Sci*, *2*(2), 119-137. https://doi.org/10.1177/2167702613497473

Castellanos-Ryan, N., Briere, F. N., O'Leary-Barrett, M., Banaschewski, T., Bokde, A., Bromberg, U., Buchel, C., Flor, H., Frouin, V., Gallinat, J., Garavan, H., Martinot, J. L., Nees, F., Paus, T., Pausova, Z., Rietschel, M., Smolka, M. N., Robbins, T. W., Whelan, R., Schumann, G., Conrod, P., & Consortium, I. (2016). The structure of psychopathology in adolescence and its common personality and cognitive correlates. *J Abnorm Psychol*, *125*(8), 1039-1052. https://doi.org/10.1037/abn0000193

Chen, J., Tam, A., Kebets, V., Orban, C., Ooi, L. Q. R., Asplund, C. L., Marek, S., Dosenbach, N. U. F., Eickhoff, S. B., Bzdok, D., Holmes, A. J., & Yeo, B. T. T. (2022). Shared and unique brain network features predict cognitive, personality, and

mental health scores in the ABCD study. *Nature Communications*, *13*(1), 2217. https://doi.org/10.1038/s41467-022-29766-8

Chini, M., & Hanganu-Opatz, I. L. (2021). Prefrontal cortex development in health and disease: lessons from rodents and humans. *Trends in Neurosciences*, *44*(3), 227-240.

Conradt, E., Crowell, S. E., & Cicchetti, D. (2021). Using development and psychopathology principles to inform the Research Domain Criteria (RDoC) framework. *Development and psychopathology*, *33*(5), 1521-1525. https://doi.org/10.1017/S0954579421000985

Davatzikos, C. (2019). Machine learning in neuroimaging: Progress and challenges. *NeuroImage*, *197*, 652.

Deacon, B. J. (2013). The biomedical model of mental disorder: A critical analysis of its validity, utility, and effects on psychotherapy research. *Clinical Psychology Review*, *33*(7), 846-861.

Dosenbach, N. U. F., Koller, J. M., Earl, E. A., Miranda-Dominguez, O., Klein, R. L., Van, A. N., Snyder, A. Z., Nagel, B. J., Nigg, J. T., Nguyen, A. L., Wesevich, V., Greene, D. J., & Fair, D. A. (2017). Real-time motion analytics during brain MRI improve data quality and reduce costs. *NeuroImage*, *161*, 80-93. https://doi.org/https://doi.org/10.1016/j.neuroimage.2017.08.025

Durbin, C. E., Wilson, S., & MacDonald III, A. W. (2022). Integrating development into the Research Domain Criteria (RDoC) framework: Introduction to the special section. *Journal of Psychopathology and Clinical Science*, *131*(6), 535.

Durham, E. L., Ghanem, K., Stier, A. J., Cardenas-Iniguez, C., Reimann, G. E., Jeong, H. J., Dupont, R. M., Dong, X., Moore, T. M., Berman, M. G., Lahey, B. B., Bzdok, D., & Kaczkurkin, A. N. (2023). Multivariate analytical approaches for investigating brain-behavior relationships [Original Research]. *Frontiers in Neuroscience*, *17*. https://doi.org/10.3389/fnins.2023.1175690

Durham, E. L., Jeong, H. J., Moore, T. M., Dupont, R. M., Cardenas-Iniguez, C., Cui, Z., Stone, F. E., Berman, M. G., Lahey, B. B., & Kaczkurkin, A. N. (2021). Association of gray matter volumes with general and specific dimensions of psychopathology in children. *Neuropsychopharmacology*, *46*(7), 1333-1339. https://doi.org/10.1038/s41386-020-00952-w

Eaton, N. R., Bringmann, L. F., Elmer, T., Fried, E. I., Forbes, M. K., Greene, A. L., Krueger, R. F., Kotov, R., McGorry, P. D., & Mei, C. (2023). A review of approaches and models in psychopathology conceptualization research. *Nature Reviews Psychology*, 1-15.

Edde, M., Leroux, G., Altena, E., & Chanraud, S. (2021). Functional brain connectivity changes across the human life span: From fetal development to old age. *Journal of Neuroscience Research*, *99*(1), 236-262. https://doi.org/https://doi.org/10.1002/jnr.24669

Elliott, M. L., Romer, A., Knodt, A. R., & Hariri, A. R. (2018). A Connectome-wide Functional Signature of Transdiagnostic Risk for Mental Illness. *Biological Psychiatry*, *84*(6), 452-459. https://doi.org/https://doi.org/10.1016/j.biopsych.2018.03.012

Esteban, O., Birman, D., Schaer, M., Koyejo, O. O., Poldrack, R. A., & Gorgolewski, K. J. (2017). MRIQC: Advancing the automatic prediction of image quality in MRI from unseen sites. *PLoS ONE*, *12*(9), e0184661. https://doi.org/10.1371/journal.pone.0184661

Esteban, O., Markiewicz, C. J., Blair, R. W., Moodie, C. A., Isik, A. I., Erramuzpe, A., Kent, J. D., Goncalves, M., DuPre, E., & Snyder, M. (2019). fMRIPrep: a robust preprocessing pipeline for functional MRI. *Nature methods*, *16*(1), 111-116.

First, M. B., Reed, G. M., Hyman, S. E., & Saxena, S. (2015). The development of the ICD-11 clinical descriptions and diagnostic guidelines for mental and behavioural disorders. *World psychiatry*, *14*(1), 82-90.

Fischl, B. (2012). FreeSurfer. *NeuroImage*, *62*(2), 774-781. https://doi.org/https://doi.org/10.1016/j.neuroimage.2012.01.021

Forbes, M. K., Neo, B., Nezami, O. M., Fried, E. I., Faure, K., Michelsen, B., Twose, M., & Dras, M. (2023). Elemental psychopathology: Distilling constituent symptoms and patterns of repetition in the diagnostic criteria of the DSM-5.

Fried, E. I. (2020). Theories and models: What they are, what they are for, and what they are about. *Psychological Inquiry*, *31*(4), 336-344.

Fried, E. I., & Nesse, R. M. (2015). Depression is not a consistent syndrome: an investigation of unique symptom patterns in the STAR* D study. *Journal of Affective Disorders*, *172*, 96-102.

Fuhrmann, D., Knoll, L. J., & Blakemore, S.-J. (2015). Adolescence as a sensitive period of brain development. *Trends in Cognitive Sciences*, *19*(10), 558-566.

Giedd, J. N., Raznahan, A., Alexander-Bloch, A., Schmitt, E., Gogtay, N., & Rapoport, J. L. (2015). Child Psychiatry Branch of the National Institute of Mental Health Longitudinal Structural Magnetic Resonance Imaging Study of Human Brain

Development. *Neuropsychopharmacology*, *40*(1), 43-49. https://doi.org/10.1038/npp.2014.236

Goodkind, M., Eickhoff, S. B., Oathes, D. J., Jiang, Y., Chang, A., Jones-Hagata, L. B., Ortega, B. N., Zaiko, Y. V., Roach, E. L., Korgaonkar, M. S., Grieve, S. M., Galatzer-Levy, I., Fox, P. T., & Etkin, A. (2015). Identification of a Common Neurobiological Substrate for Mental Illness. *JAMA Psychiatry*, *72*(4), 305-315. https://doi.org/10.1001/jamapsychiatry.2014.2206

Goodman, R. (1997). The Strengths and Difficulties Questionnaire: a research note. *Journal of Child Psychology and Psychiatry*, *38*(5), 581-586.

Gur, R. C., Calkins, M. E., Satterthwaite, T. D., Ruparel, K., Bilker, W. B., Moore, T. M., Savitt, A. P., Hakonarson, H., & Gur, R. E. (2014). Neurocognitive growth charting in psychosis spectrum youths. *JAMA Psychiatry*, *71*(4), 366-374.

Hasin, D., & Kilcoyne, B. (2012). Comorbidity of psychiatric and substance use disorders in the United States: current issues and findings from the NESARC. *Current opinion in psychiatry*, *25*(3), 165.

Haslam, N., McGrath, M. J., Viechtbauer, W., & Kuppens, P. (2020). Dimensions over categories: a meta-analysis of taxometric research. *Psychological medicine*, *50*(9), 1418-1432. https://doi.org/10.1017/S003329172000183X

Hettwer, M. D., Larivière, S., Park, B. Y., van den Heuvel, O. A., Schmaal, L., Andreassen, O. A., Ching, C. R. K., Hoogman, M., Buitelaar, J., van Rooij, D., Veltman, D. J., Stein, D. J., Franke, B., van Erp, T. G. M., van Rooij, D., van den Heuvel, O. A., van Erp, T. G. M., Jahanshad, N., Thompson, P. M., Thomopoulos, S. I., Bethlehem, R. A. I., Bernhardt, B. C., Eickhoff, S. B., Valk, S. L., Group, E. A. W., Group, E. A. W., Group, E. B. D. W., Group, E. M. D. W., Group, E. O. W., & Group, E. S. W. (2022). Coordinated cortical thickness alterations across six neurodevelopmental and psychiatric disorders. *Nature Communications*, *13*(1), 6851. https://doi.org/10.1038/s41467-022-34367-6

Hong, J., Hwang, J., & Lee, J.-H. (2023). General psychopathology factor (p-factor) prediction using resting-state functional connectivity and a scanner-generalization neural network. *Journal of Psychiatric Research*, *158*, 114-125. https://doi.org/https://doi.org/10.1016/j.jpsychires.2022.12.037

Hooks, B. M., & Chen, C. (2007). Critical periods in the visual system: changing views for a model of experience-dependent plasticity. *Neuron*, *56*(2), 312-326.

Hyman, S. E. (2007). Can neuroscience be integrated into the DSM-V? *Nature Reviews Neuroscience*, *8*(9), 725-732.

Hyman, S. E. (2021). Psychiatric disorders: Grounded in human biology but not natural kinds. *Perspectives in Biology and Medicine*, *64*(1), 6-28.

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., Sanislow, C., & Wang, P. (2010). Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *167*, 748-751.

Insel, T. R. (2010). Rethinking schizophrenia. *Nature*, *468*(7321), 187-193. https://doi.org/10.1038/nature09552

Jadavji, N. M., Haelterman, N. A., Sud, R., & Antonietti, A. (2023). Editorial: Reproducibility in neuroscience [Editorial]. *Frontiers in Integrative Neuroscience*, *17*. https://doi.org/10.3389/fnint.2023.1271818

Kaczkurkin, A. N., Moore, T. M., Sotiras, A., Xia, C. H., Shinohara, R. T., & Satterthwaite, T. D. (2020). Approaches to Defining Common and Dissociable Neurobiological Deficits Associated With Psychopathology in Youth. *Biological Psychiatry*, *88*(1), 51-62. https://doi.org/https://doi.org/10.1016/j.biopsych.2019.12.015

Kaczkurkin, A. N., Park, S. S., Sotiras, A., Moore, T. M., Calkins, M. E., Cieslak, M., Rosen, A. F. G., Ciric, R., Xia, C. H., Cui, Z., Sharma, A., Wolf, D. H., Ruparel, K., Pine, D. S., Shinohara, R. T., Roalf, D. R., Gur, R. C., Davatzikos, C., Gur, R. E., & Satterthwaite, T. D. (2019). Evidence for Dissociable Linkage of Dimensions of Psychopathology to Brain Structure in Youths. *American Journal of Psychiatry*, *176*(12), 1000-1009. https://doi.org/10.1176/appi.ajp.2019.18070835

Karcher, N. R., Michelini, G., Kotov, R., & Barch, D. M. (2021). Associations Between Resting-State Functional Connectivity and a Hierarchical Dimensional Structure of Psychopathology in Middle Childhood. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *6*(5), 508-517. https://doi.org/https://doi.org/10.1016/j.bpsc.2020.09.008

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

Kaufmann, T., Alnaes, D., Doan, N. T., Brandt, C. L., Andreassen, O. A., & Westlye, L. T. (2017). Delayed stabilization and individualization in connectome development are

related to psychiatric disorders. *Nature Neuroscience*, *20*(4), 513-515. https://doi.org/10.1038/nn.4511

Kebets, V., Holmes, A. J., Orban, C., Tang, S., Li, J., Sun, N., Kong, R., Poldrack, R. A., & Yeo, B. T. T. (2019). Somatosensory-Motor Dysconnectivity Spans Multiple Transdiagnostic Dimensions of Psychopathology. *Biological Psychiatry*, *86*(10), 779-791. https://doi.org/https://doi.org/10.1016/j.biopsych.2019.06.013

Kebets, V., Piguet, C., Chen, J., Ooi, L. Q. R., Kirschner, M., Siffredi, V., Misic, B., Yeo, B. T., & Bernhardt, B. (2023). Multimodal neural correlates of childhood psychopathology. *bioRxiv*, 2023.2003. 2002.530821.

Kendell, R. E. (1989). Clinical validity. *Psychological medicine*, *19*(1), 45-55.

Kendler, K. S. (2016). The nature of psychiatric disorders. *World psychiatry*, *15*(1), 5-12.

Kessler, R. C., Angermeyer, M., Anthony, J. C., De Graaf, R., Demyttenaere, K., Gasquet, I., De Girolamo, G., Gluzman, S., Gureje, O., & Haro, J. M. (2007). Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. *World psychiatry*, *6*(3), 168.

Kim, S.-G., & Ogawa, S. (2012). Biophysical and Physiological Origins of Blood Oxygenation Level-Dependent fMRI Signals. *Journal of Cerebral Blood Flow & Metabolism*, *32*(7), 1188-1206. https://doi.org/10.1038/jcbfm.2012.23

Kjelkenes, R., Wolfers, T., Alnæs, D., van der Meer, D., Pedersen, M. L., Dahl, A., Voldsbekk, I., Moberget, T., Tamnes, C. K., Andreassen, O. A., Marquand, A. F., & Westlye, L. T. (2022). Mapping normative trajectories of cognitive function and its relation to psychopathology symptoms and genetic risk in youth. *Biological Psychiatry: Global Open Science*. https://doi.org/10.1016/j.bpsgos.2022.01.007

Knudsen, E. I. (2004). Sensitive periods in the development of the brain and behavior. *Journal of cognitive neuroscience*, *16*(8), 1412-1425.

Kotov, R., Krueger, R. F., Watson, D., Achenbach, T. M., Althoff, R. R., Bagby, R. M., Brown, T. A., Carpenter, W. T., Caspi, A., & Clark, L. A. (2017). The Hierarchical Taxonomy of Psychopathology (HiTOP): A dimensional alternative to traditional nosologies. *Journal of abnormal psychology*, *126*(4), 454.

Krishnan, A., Williams, L. J., McIntosh, A. R., & Abdi, H. (2011). Partial Least Squares (PLS) methods for neuroimaging: A tutorial and review. *NeuroImage*, *56*(2), 455-475. https://doi.org/https://doi.org/10.1016/j.neuroimage.2010.07.034

Lahey, B. B., Applegate, B., Hakes, J. K., Zald, D. H., Hariri, A. R., & Rathouz, P. J. (2012). Is there a general factor of prevalent psychopathology during adulthood? *Journal of abnormal psychology*, *121*(4), 971-977. https://doi.org/10.1037/a0028355

Lahey, B. B., Lee, S. S., Sibley, M. H., Applegate, B., Molina, B. S., & Pelham, W. E. (2016). Predictors of adolescent outcomes among 4–6-year-old children with attention-deficit/hyperactivity disorder. *Journal of abnormal psychology*, *125*(2), 168.

Larsen, B., & Luna, B. (2018). Adolescence as a neurobiological critical period for the development of higher-order cognition. *Neuroscience & Biobehavioral Reviews*, *94*, 179-195. https://doi.org/10.1016/J.NEUBIOREV.2018.09.005

Lees, B., Squeglia, L. M., McTeague, L. M., Forbes, M. K., Krueger, R. F., Sunderland, M., Baillie, A. J., Koch, F., Teesson, M., & Mewton, L. (2021). Altered Neurocognitive Functional Connectivity and Activation Patterns Underlie Psychopathology in Preadolescence. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *6*(4), 387-398. https://doi.org/https://doi.org/10.1016/j.bpsc.2020.09.007

Lehman, B. J., David, D. M., & Gruber, J. A. (2017). Rethinking the biopsychosocial model of health: Understanding health as a dynamic system. *Social and Personality Psychology Compass*, *11*(8), e12328. https://doi.org/https://doi.org/10.1111/spc3.12328

Linke, J. O., Abend, R., Kircanski, K., Clayton, M., Stavish, C., Benson, B. E., Brotman, M. A., Renaud, O., Smith, S. M., Nichols, T. E., Leibenluft, E., Winkler, A. M., & Pine, D. S. (2021). Shared and Anxiety-Specific Pediatric Psychopathology Dimensions Manifest Distributed Neural Correlates. *Biological Psychiatry*, *89*(6), 579-587. https://doi.org/10.1016/j.biopsych.2020.10.018

Lynch, S. J., Sunderland, M., Newton, N. C., & Chapman, C. (2021). A systematic review of transdiagnostic risk and protective factors for general and specific psychopathology in young people. *Clinical Psychology Review*, *87*, 102036. https://doi.org/https://doi.org/10.1016/j.cpr.2021.102036

Marek, S., Tervo-Clemmens, B., Calabro, F. J., Montez, D. F., Kay, B. P., Hatoum, A. S., Donohue, M. R., Foran, W., Miller, R. L., Hendrickson, T. J., Malone, S. M., Kandala, S., Feczko, E., Miranda-Dominguez, O., Graham, A. M., Earl, E. A., Perrone, A. J., Cordova, M., Doyle, O., Moore, L. A., Conan, G. M., Uriarte, J., Snider, K., Lynch, B. J., Wilgenbusch, J. C., Pengo, T., Tam, A., Chen, J., Newbold, D. J., Zheng, A., Seider, N. A., Van, A. N., Metoki, A., Chauvin, R. J., Laumann, T. O., Greene, D. J., Petersen, S. E., Garavan, H., Thompson, W. K., Nichols, T. E., Yeo, B. T. T., Barch, D.

M., Luna, B., Fair, D. A., & Dosenbach, N. U. F. (2022). Reproducible brain-wide association studies require thousands of individuals. *Nature*, *603*(7902), 654-660. https://doi.org/10.1038/s41586-022-04492-9

Masten, A. S., & Cicchetti, D. (2010). Developmental cascades. *Development and psychopathology*, *22*(3), 491-495.

MathWorks. (2020). *MATLAB*. In

McIntosh, A. R., & Lobaugh, N. J. (2004). Partial least squares analysis of neuroimaging data: applications and advances. *NeuroImage*, *23*, S250-S263.

McTeague, L. M., Huemer, J., Carreon, D. M., Jiang, Y., Eickhoff, S. B., & Etkin, A. (2017). Identification of Common Neural Circuit Disruptions in Cognitive Control Across Psychiatric Disorders. *American Journal of Psychiatry*, *174*(7), 676-685. https://doi.org/10.1176/appi.ajp.2017.16040400

McTeague, L. M., Rosenberg, B. M., Lopez, J. W., Carreon, D. M., Huemer, J., Jiang, Y., Chick, C. F., Eickhoff, S. B., & Etkin, A. (2020). Identification of common neural circuit disruptions in emotional processing across psychiatric disorders. *American Journal of Psychiatry*, *177*(5), 411-421.

Mewton, L., Lees, B., Squeglia, L. M., Forbes, M. K., Sunderland, M., Krueger, R., Koch, F. C., Baillie, A., Slade, T., Hoy, N., & Teesson, M. (2022). The relationship between brain structure and general psychopathology in preadolescents. *Journal of Child Psychology and Psychiatry*, *63*(7), 734-744. https://doi.org/https://doi.org/10.1111/jcpp.13513

Michelini, G., Barch, D. M., Tian, Y., Watson, D., Klein, D. N., & Kotov, R. (2019). Delineating and validating higher-order dimensions of psychopathology in the Adolescent Brain Cognitive Development (ABCD) study. *Translational Psychiatry*, *9*(1), 261. https://doi.org/10.1038/s41398-019-0593-4

Miller, K. L., Alfaro-Almagro, F., Bangerter, N. K., Thomas, D. L., Yacoub, E., Xu, J., Bartsch, A. J., Jbabdi, S., Sotiropoulos, S. N., Andersson, J. L., Griffanti, L., Douaud, G., Okell, T. W., Weale, P., Dragonu, I., Garratt, S., Hudson, S., Collins, R., Jenkinson, M., Matthews, P. M., & Smith, S. M. (2016). Multimodal population brain imaging in the UK Biobank prospective epidemiological study. *Nat Neurosci*, *19*(11), 1523-1536. https://doi.org/10.1038/nn.4393

Mills, K. L., Goddings, A.-L., Herting, M. M., Meuwese, R., Blakemore, S.-J., Crone, E. A., Dahl, R. E., Güroğlu, B., Raznahan, A., & Sowell, E. R. (2016). Structural brain

development between childhood and adulthood: Convergence across four longitudinal samples. *NeuroImage*, *141*, 273-281.

Moberget, T., Alnæs, D., Kaufmann, T., Doan, N. T., Córdova-Palomera, A., Norbom, L. B., Rokicki, J., van der Meer, D., Andreassen, O. A., & Westlye, L. T. (2019). Cerebellar Gray Matter Volume Is Associated With Cognitive Function and Psychopathology in Adolescence. *Biological Psychiatry*, *86*(1), 65-75. https://doi.org/https://doi.org/10.1016/j.biopsych.2019.01.019

Modabbernia, A., Janiri, D., Doucet, G. E., Reichenberg, A., & Frangou, S. (2021). Multivariate Patterns of Brain-Behavior-Environment Associations in the Adolescent Brain and Cognitive Development Study. *Biological Psychiatry*, *89*(5), 510-520. https://doi.org/https://doi.org/10.1016/j.biopsych.2020.08.014

Modabbernia, A., Reichenberg, A., Ing, A., Moser, D. A., Doucet, G. E., Artiges, E., Banaschewski, T., Barker, G. J., Becker, A., Bokde, A. L. W., Quinlan, E. B., Desrivières, S., Flor, H., Fröhner, J. H., Garavan, H., Gowland, P., Grigis, A., Grimmer, Y., Heinz, A., Insensee, C., Ittermann, B., Martinot, J.-L., Martinot, M.-L. P., Millenet, S., Nees, F., Orfanos, D. P., Paus, T., Penttilä, J., Poustka, L., Smolka, M. N., Stringaris, A., van Noort, B. M., Walter, H., Whelan, R., Schumann, G., Frangou, S., & Consortium, I. (2021). Linked patterns of biological and environmental covariation with brain structure in adolescence: a population-based longitudinal study. *Molecular Psychiatry*, *26*(9), 4905-4918. https://doi.org/10.1038/s41380-020-0757-x

Moore, T. M., Reise, S. P., Gur, R. E., Hakonarson, H., & Gur, R. C. (2015). Psychometric properties of the Penn Computerized Neurocognitive Battery. *Neuropsychology*, *29*(2), 235.

Murray, R. M., Bhavsar, V., Tripoli, G., & Howes, O. (2017). 30 Years on: How the Neurodevelopmental Hypothesis of Schizophrenia Morphed Into the Developmental Risk Factor Model of Psychosis. *Schizophrenia Bulletin*, *43*(6), 1190-1196. https://doi.org/10.1093/schbul/sbx121

Nielsen, A. N., Barch, D. M., Petersen, S. E., Schlaggar, B. L., & Greene, D. J. (2020). Machine learning with neuroimaging: Evaluating its applications in psychiatry. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *5*(8), 791-798.

Nour, M. M., Liu, Y., & Dolan, R. J. (2022). Functional neuroimaging in psychiatry and the case for failing better. *Neuron*, *110*(16), 2524-2544.

Opel, N., Goltermann, J., Hermesdorf, M., Berger, K., Baune, B. T., & Dannlowski, U. (2020). Cross-Disorder Analysis of Brain Structural Abnormalities in Six Major

Psychiatric Disorders: A Secondary Analysis of Mega- and Meta-analytical Findings From the ENIGMA Consortium. *Biological Psychiatry*, *88*(9), 678-686. https://doi.org/https://doi.org/10.1016/j.biopsych.2020.04.027

Organization, W. H. (1992). *The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines* (Vol. 1). World Health Organization.

Parkes, L., Moore, T. M., Calkins, M. E., Cook, P. A., Cieslak, M., Roalf, D. R., Wolf, D. H., Gur, R. C., Gur, R. E., Satterthwaite, T. D., & Bassett, D. S. (2021). Transdiagnostic dimensions of psychopathology explain individuals' unique deviations from normative neurodevelopment in brain structure. *Translational Psychiatry*, *11*(1), 232. https://doi.org/10.1038/s41398-021-01342-6

Paus, T., Keshavan, M., & Giedd, J. N. (2008). Why do many psychiatric disorders emerge during adolescence? *Nature Reviews Neuroscience*, *9*(12), 947-957. https://www.nature.com/articles/nrn2513.pdf

Poldrack, R. A., Huckins, G., & Varoquaux, G. (2020). Establishment of best practices for evidence for prediction: a review. *JAMA Psychiatry*, *77*(5), 534-540.

Power, J. D., Fair, D. A., Schlaggar, B. L., & Petersen, S. E. (2010). The development of human functional brain networks. *Neuron*, *67*(5), 735-748.

Raichle, M. E. (1987). Circulatory and metabolic correlates of brain function in normal humans. *Higher functions of the brain*.

Reh, R. K., Dias, B. G., Nelson III, C. A., Kaufer, D., Werker, J. F., Kolb, B., Levine, J. D., & Hensch, T. K. (2020). Critical period regulation across multiple timescales. *Proceedings of the National Academy of Sciences*, *117*(38), 23242-23251.

Romer, A. L., Elliott, M. L., Knodt, A. R., Sison, M. L., Ireland, D., Houts, R., Ramrakha, S., Poulton, R., Keenan, R., Melzer, T. R., Moffitt, T. E., Caspi, A., & Hariri, A. R. (2020). Pervasively Thinner Neocortex as a Transdiagnostic Feature of General Psychopathology. *American Journal of Psychiatry*, *178*(2), 174-182. https://doi.org/10.1176/appi.ajp.2020.19090934

Romer, A. L., Knodt, A. R., Houts, R., Brigidi, B. D., Moffitt, T. E., Caspi, A., & Hariri, A. R. (2018). Structural alterations within cerebellar circuitry are associated with general liability for common mental disorders. *Molecular Psychiatry*, *23*(4), 1084-1090. https://doi.org/10.1038/mp.2017.57

Romer, A. L., Knodt, A. R., Sison, M. L., Ireland, D., Houts, R., Ramrakha, S., Poulton, R., Keenan, R., Melzer, T. R., Moffitt, T. E., Caspi, A., & Hariri, A. R. (2021). Replicability of structural brain alterations associated with general psychopathology:

evidence from a population-representative birth cohort. *Molecular Psychiatry*, *26*(8), 3839-3846. https://doi.org/10.1038/s41380-019-0621-z

Romer, A. L., Ren, B., & Pizzagalli, D. A. (2023). Brain Structure Relations With Psychopathology Trajectories in the ABCD Study. *Journal of the American Academy of Child & Adolescent Psychiatry*, *62*(8), 895-907. https://doi.org/https://doi.org/10.1016/j.jaac.2023.02.002

Ruggero, C. J., Kotov, R., Hopwood, C. J., First, M., Clark, L. A., Skodol, A. E., Mullins-Sweatt, S. N., Patrick, C. J., Bach, B., & Cicero, D. C. (2019). Integrating the Hierarchical Taxonomy of Psychopathology (HiTOP) into clinical practice. *Journal of consulting and clinical psychology*, *87*(12), 1069.

Saggar, M., & Uddin, L. Q. (2019). Pushing the boundaries of psychiatric neuroimaging to ground diagnosis in biology. *eNeuro*, *6*(6).

Satterthwaite, T. D., Connolly, J. J., Ruparel, K., Calkins, M. E., Jackson, C., Elliott, M. A., Roalf, D. R., Hopson, R., Prabhakaran, K., Behr, M., Qiu, H., Mentch, F. D., Chiavacci, R., Sleiman, P. M. A., Gur, R. C., Hakonarson, H., & Gur, R. E. (2016). The Philadelphia Neurodevelopmental Cohort: A publicly available resource for the study of normal and abnormal brain development in youth. *NeuroImage*, *124*(Pt B), 1115-1119. https://doi.org/10.1016/j.neuroimage.2015.03.056

Schaefer, A., Kong, R., Gordon, E. M., Laumann, T. O., Zuo, X.-N., Holmes, A. J., Eickhoff, S. B., & Yeo, B. T. T. (2018). Local-Global Parcellation of the Human Cerebral Cortex from Intrinsic Functional Connectivity MRI. *Cerebral Cortex*, *28*(9), 3095-3114. https://doi.org/10.1093/cercor/bhx179

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

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., Bannister, P. R., De Luca, M., Drobnjak, I., Flitney, D. E., Niazy, R. K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J. M., & Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, *23*, 208-219. https://doi.org/10.1016/j.neuroimage.2004.07.051

Smith, S. M., Nichols, T. E., Vidaurre, D., Winkler, A. M., Behrens, T. E. J., Glasser, M. F., Ugurbil, K., Barch, D. M., Van Essen, D. C., & Miller, K. L. (2015). A positive-negative mode of population covariation links brain connectivity, demographics and behavior. *Nature Neuroscience*, *18*(11), 1565-1567. https://doi.org/10.1038/nn.4125

Snyder, H. R., Hankin, B. L., Sandman, C. A., Head, K., & Davis, E. P. (2017). Distinct Patterns of Reduced Prefrontal and Limbic Gray Matter Volume in Childhood General and Internalizing Psychopathology. *Clinical Psychological Science*, *5*(6), 1001-1013. https://doi.org/10.1177/2167702617714563

Solmi, M., Radua, J., Olivola, M., Croce, E., Soardo, L., Salazar de Pablo, G., Il Shin, J., Kirkbride, J. B., Jones, P., & Kim, J. H. (2022). Age at onset of mental disorders worldwide: large-scale meta-analysis of 192 epidemiological studies. *Molecular Psychiatry*, *27*(1), 281-295.

Sprooten, E., Franke, B., & Greven, C. U. (2022). The P-factor and its genomic and neural equivalents: an integrated perspective. *Molecular Psychiatry*, *27*(1), 38-48.

Sydnor, V. J., Larsen, B., Bassett, D. S., Alexander-Bloch, A., Fair, D. A., Liston, C., Mackey, A. P., Milham, M. P., Pines, A., & Roalf, D. R. (2021). Neurodevelopment of the association cortices: Patterns, mechanisms, and implications for psychopathology. *Neuron*, *109*(18), 2820-2846.

Tamnes, C. K., Herting, M. M., Goddings, A.-L., Meuwese, R., Blakemore, S.-J., Dahl, R. E., Güroğlu, B., Raznahan, A., Sowell, E. R., Crone, E. A., & Mills, K. L. (2017). Development of the Cerebral Cortex across Adolescence: A Multisample Study of Inter-Related Longitudinal Changes in Cortical Volume, Surface Area, and Thickness. *The Journal of Neuroscience*, *37*(12), 3402. https://doi.org/10.1523/JNEUROSCI.3302-16.2017

Team, R. C. (2018). *R: A language and environment for statistical computing*. In http://www.r-project.org/.

Traut, N., Heuer, K., Lemaître, G., Beggiato, A., Germanaud, D., Elmaleh, M., Bethegnies, A., Bonnasse-Gahot, L., Cai, W., & Chambon, S. (2022). Insights from an autism imaging biomarker challenge: promises and threats to biomarker discovery. *NeuroImage*, *255*, 119171.

Uddin, L., Supekar, K., & Menon, V. (2013). Reconceptualizing functional brain connectivity in autism from a developmental perspective [Review]. *Frontiers in Human Neuroscience*, *7*. https://doi.org/10.3389/fnhum.2013.00458

Uddin, L. Q., Dajani, D. R., Voorhies, W., Bednarz, H., & Kana, R. K. (2017). Progress and roadblocks in the search for brain-based biomarkers of autism and attention-deficit/hyperactivity disorder. *Translational Psychiatry*, *7*(8), e1218-e1218. https://doi.org/10.1038/tp.2017.164

Uhlhaas, P. J., Davey, C. G., Mehta, U. M., Shah, J., Torous, J., Allen, N. B., Avenevoli, S., Bella-Awusah, T., Chanen, A., Chen, E. Y. H., Correll, C. U., Do, K. Q., Fisher, H. L., Frangou, S., Hickie, I. B., Keshavan, M. S., Konrad, K., Lee, F. S., Liu, C. H., Luna, B., McGorry, P. D., Meyer-Lindenberg, A., Nordentoft, M., Öngür, D., Patton, G. C., Paus, T., Reininghaus, U., Sawa, A., Schoenbaum, M., Schumann, G., Srihari, V. H., Susser, E., Verma, S. K., Woo, T. W., Yang, L. H., Yung, A. R., & Wood, S. J. (2023). Towards a youth mental health paradigm: a perspective and roadmap. *Molecular Psychiatry*. https://doi.org/10.1038/s41380-023-02202-z

Vanes, L. D., & Dolan, R. J. (2021). Transdiagnostic neuroimaging markers of psychiatric risk: A narrative review. *NeuroImage: Clinical*, *30*, 102634. https://doi.org/https://doi.org/10.1016/j.nicl.2021.102634

Varoquaux, G. (2018). Cross-validation failure: Small sample sizes lead to large error bars. *NeuroImage*, *180*, 68-77.

Walhovd, K. B., Johansen-Berg, H., & Káradóttir, R. T. (2014). Unraveling the secrets of white matter - Bridging the gap between cellular, animal and human imaging studies. *Neuroscience*, *276*, 2-13. https://doi.org/10.1016/j.neuroscience.2014.06.058

Walhovd, K. B., Lövden, M., & Fjell, A. M. (2023). Timing of lifespan influences on brain and cognition. *Trends in Cognitive Sciences*, *27*(10), 901-915. https://doi.org/10.1016/j.tics.2023.07.001

Wang, H.-T., Smallwood, J., Mourao-Miranda, J., Xia, C. H., Satterthwaite, T. D., Bassett, D. S., & Bzdok, D. (2020). Finding the needle in a high-dimensional haystack: Canonical correlation analysis for neuroscientists. *NeuroImage*, *216*, 116745. https://doi.org/https://doi.org/10.1016/j.neuroimage.2020.116745

Weishaupt, D., Köchli, V. D., Marincek, B., Froehlich, J. M., Nanz, D., & Pruessmann, K. P. (2006). *How does MRI work?: an introduction to the physics and function of magnetic resonance imaging* (Vol. 2). Springer.

Winter, N. R., Leenings, R., Ernsting, J., Sarink, K., Fisch, L., Emden, D., Blanke, J., Goltermann, J., Opel, N., & Barkhau, C. (2022). Quantifying deviations of brain structure and function in major depressive disorder across neuroimaging modalities. *JAMA Psychiatry*, *79*(9), 879-888.

Woo, C.-W., Chang, L. J., Lindquist, M. A., & Wager, T. D. (2017). Building better biomarkers: brain models in translational neuroimaging. *Nature Neuroscience*, *20*(3), 365-377.

Xia, C. H., Ma, Z., Ciric, R., Gu, S., Betzel, R. F., Kaczkurkin, A. N., Calkins, M. E., Cook, P. A., García de la Garza, A., Vandekar, S. N., Cui, Z., Moore, T. M., Roalf, D. R., Ruparel, K., Wolf, D. H., Davatzikos, C., Gur, R. C., Gur, R. E., Shinohara, R. T., Bassett, D. S., & Satterthwaite, T. D. (2018). Linked dimensions of psychopathology and connectivity in functional brain networks. *Nature Communications*, *9*(1), 3003. https://doi.org/10.1038/s41467-018-05317-y

Xiao, X., Hammond, C., Salmeron, B. J., Wang, D., Gu, H., Zhai, T., Nguyen, H., Lu, H., Ross, T. J., & Yang, Y. (2023). Brain Functional Connectome Defines a Transdiagnostic Dimension Shared by Cognitive Function and Psychopathology in Preadolescents. *Biological Psychiatry*. https://doi.org/https://doi.org/10.1016/j.biopsych.2023.08.028

Xie, C., Xiang, S., Shen, C., Peng, X., Kang, J., Li, Y., Cheng, W., He, S., Bobou, M., Broulidakis, M. J., van Noort, B. M., Zhang, Z., Robinson, L., Vaidya, N., Winterer, J., Zhang, Y., King, S., Banaschewski, T., Barker, G. J., Bokde, A. L. W., Bromberg, U., Büchel, C., Flor, H., Grigis, A., Garavan, H., Gowland, P., Heinz, A., Ittermann, B., Lemaître, H., Martinot, J.-L., Martinot, M.-L. P., Nees, F., Orfanos, D. P., Paus, T., Poustka, L., Fröhner, J. H., Schmidt, U., Sinclair, J., Smolka, M. N., Stringaris, A., Walter, H., Whelan, R., Desrivières, S., Sahakian, B. J., Robbins, T. W., Schumann, G., Jia, T., Feng, J., van Noort, B. M., Consortium, I., Consortium, S. E., & Consortium, Z. I. B. (2023). A shared neural basis underlying psychiatric comorbidity. *Nature Medicine*, *29*(5), 1232-1242. https://doi.org/10.1038/s41591-023-02317-4

Yeo, B. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., Roffman, J. L., Smoller, J. W., Zöllei, L., & Polimeni, J. R. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of neurophysiology*.

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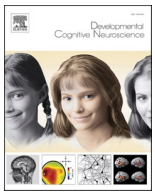

Shared pattern of impaired social communication and cognitive ability in the youth brain across diagnostic boundaries

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ABSTRACT

Background: Abnormalities in brain structure are shared across diagnostic categories. Given the high rate of comorbidity, the interplay of relevant behavioural factors may also cross these classic boundaries.
Methods: We aimed to detect brain-based dimensions of behavioural factors using canonical correlation and independent component analysis in a clinical youth sample (n = 1732, 64 % male, age: 5–21 years).
Results: We identified two correlated patterns of brain structure and behavioural factors. The first mode reflected physical and cognitive maturation ($r = 0.92$, $p = .005$). The second mode reflected lower cognitive ability, poorer social skills, and psychological difficulties ($r = 0.92$, $p = .006$). Elevated scores on the second mode were a common feature across all diagnostic boundaries and linked to the number of comorbid diagnoses independently of age. Critically, this brain pattern predicted normative cognitive deviations in an independent population-based sample (n = 1253, 54 % female, age: 8–21 years), supporting the generalisability and external validity of the reported brain-behaviour relationships.
Conclusions: These results reveal dimensions of brain-behaviour associations across diagnostic boundaries, highlighting potent disorder-general patterns as the most prominent. In addition to providing biologically informed patterns of relevant behavioural factors for mental illness, this contributes to a growing body of evidence in favour of transdiagnostic approaches to prevention and intervention.

1. Introduction

Mental illness typically manifest during childhood or adolescence (Caspi et al., 2020; Kessler et al., 2007), alluding to the importance of neurodevelopment for mental health. The interplay of a multitude of factors likely shapes the neurodevelopmental trajectory; however, most studies have typically investigated only one or a few such factors at a time. Associations that are relevant for brain development may in turn be elevated in clinical populations and subsequently relevant for psychopathology. A comprehensive mapping of behavioural factors and how they relate to measures of brain structure in a clinical sample of youth represents a critical step towards understanding the role of neurodevelopment in health and disease.

Empirically derived models of psychopathology point to common

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symptomatology (i.e. general vulnerability) across classic diagnostic categories. In line with this, abnormalities in both genetics (Lahey et al., 2011; Pettersson et al., 2016; Roelfs et al., 2021), brain structure (Goodkind et al., 2015; Opel et al., 2020) and cognition (Abramovitch et al., 2021; Caspi et al., 2014) are shared across diagnostic syndromes. Furthermore, general psychopathology is linked to deviations from normative cortical (Parkes et al., 2021) and cognitive (Kjelkenes et al., 2022) development, pointing to the relevance of mapping associated behavioural factors across diagnostic boundaries during neurodevelopment.

Multivariate approaches in adults reveal a positive-negative population dimension linking brain features with lifestyle, demographic, and psychometric measures (Smith et al., 2015), in which factors typically considered positive are linked to advantageous or healthy brain features, while negative factors exhibit the opposite pattern. This "positive--negative" axis of covariation has since been reported in studies of adolescents (Modabbernia et al., 2021a) and children (Alnæs et al., 2020; Modabbernia et al., 2021b), alluding to the presence of a link between brain and behaviour for advantageous development already early in life. However, the distribution of such brain-behaviour associations in relation to psychopathology is not well mapped. Investigating brain-behaviour associations in a clinical population of youth may elucidate the relevance of such patterns for mental health.

Symptoms of anxiety, irritability, and attention-deficit hyperactivity disorder (ADHD) have in a previous study been linked to both shared and unique patterns of brain connectivity (Linke et al., 2021). This finding was replicated across two independent clinical samples of youth, suggesting both disorder-general and disorder-specific patterns of psychopathology in the youth brain. Across children with and without an ADHD diagnosis (Ball et al., 2018), higher ADHD symptom load was linked with poorer academic performance, delayed pubertal development, and regional variability in cortical brain structure. However, less is known about how such patterns vary across diagnostic boundaries (Lynch et al., 2021). Identification of shared and distinct patterns of brain-behaviour associations across diagnostic boundaries may provide more informed models of psychopathology, illuminating the role of neurodevelopment and brain-behaviour associations. Such patterns can be determined by utilising multivariate approaches and dimensional clinical and behavioural phenotypes, as employed in several recent studies (Smith et al., 2015; Modabbernia et al., 2021a, 2021b; Alnæs et al., 2020). However, few studies have employed this approach in clinical youth samples, thus the relevance of the reported brain-behaviour relationships remain to be determined.

In the current study we used canonical correlation analysis (CCA) in a sample of youth where the majority had at least one diagnosed psychiatric disorder. The aim was to identify latent dimensions of associations between brain structure and clinical, cognitive, and socio-environmental factors, and to reveal putative and empirically estimated cross-diagnostic and diagnosis-specific factors. By using symptom scores instead of categorical diagnostic information when decomposing the data, we modelled brain associations with dimensional measures of psychopathology (Caspi et al., 2014). Diagnostic information was used to assess the relevance of the detected patterns for clinical diagnosis. To improve interpretability (Smith et al., 2015; Alnæs et al., 2020; Miller et al., 2016), we submitted the CCA scores to independent component analysis (ICA). This procedure results in maximally correlated, maximally interpretable latent dimensions (i.e. modes) across the two high-dimensional datasets. As such, these dimensions link a broad range of behavioural factors that are present across diagnostic boundaries to individual differences in brain structure. If specific brain-behaviour patterns related to each diagnostic category exist, we expected these to appear as distinct modes for each diagnosis. While instead, if the strongest pattern is a cross-diagnostic vulnerability to psychopathology, we expected the analysis to yield one general clinical mode across diagnostic categories.

Finally, we assessed the generalisability and construct validity (Chaytor and Schmitter-Edgecombe, 2003) of the identified clinical brain pattern in an independent population-based sample. First, we derived out-of-sample brain scores using overlapping brain-imaging measures derived from a harmonised protocol across the two samples. We then associated these out-of-sample brain-scores to measures of overlapping clinical and cognitive constructs in the independent sample.

2. Materials and methods

2.1. Sample

We accessed brian structural, clinical, cognitive, and socio-environmental variables from the Healthy Brain Network (HBN) (Alexander et al., 2017), a cohort consisting of children and adolescents from New York City, USA aged 5–21. The data collection is currently ongoing, with behavioural data from 3628 individuals and magnetic resonance imaging (MRI) data from 2645 individuals having been released by the time of analyses for this study. Individuals were recruited through community sampling in which children with clinical concerns were encouraged to participate. Then, they underwent extensive assessment of biological and behavioural characteristics, such as neuroimaging, neuropsychological testing, psychiatric evaluation, genetics, physical assessment, and interviews regarding environmental, demographical and lifestyle factors. After quality control and data cleaning (described in Section 2.2), the final sample, with both MRI and behavioural data available, consisted of 1732 participants (624 females; mean ± sd age: 10.52 ± 3.17 years). Sample demographics are provided in Fig. 1.

2.2. Data pre-processing

Behavioural data from 3628 participants in HBN were processed using R (https://cran.r-project.org). Categorical diagnostic information was removed from the data, keeping only symptom scores. Then variables were cleaned for extreme scores and large amounts of missing data (remaining n = 2603). See Supplementary methods in the Supplementary Material for more detail. MRI measures were obtained from T_1-weighted scans of 2645 participants. Quality assurance was performed using the MRIQC classifier (Esteban et al., 2017) (n = 2479). For participants with more than one T_1-weighted scan sequence, we selected the sequence with the best estimated quality. Distributions of imaging quality across scan sequences are shown in Fig. S1.

The selected T_1-weighted data were then processed using FreeSurfer (Fischl, 2012; Iglesias et al., 2015a, 2015b, 2018; Saygin et al., 2017; Billot et al., 2020) (see Supp. methods). We extracted cortical thickness, area, and volume for 34 regions of interest per hemisphere using the Desikan-Killiany parcellation, in addition to gyrification indices, nuclei/subfield and subcortical volumes, as well as summary statistics (n = 2440). Next, MRI variables were cleaned and quality controlled (n = 2379, see Supp. methods) and the remaining variables residualised for scanner/site, and T_1-weighted scan sequence. Volumetric features were residualised for estimated total intracranial volume (eTIV). To also capture associations with global volume, eTIV was included as a variable in the analysis. Both for behavioural and MRI data, remaining missing values were imputed with *knnimpute* and data was normalised using a rank-based normal transformation (*palm_inormal*) from FMRIB Software Library Permutation Analysis of Linear Models (Winkler et al., 2014). The final sample, with both behavioural and MRI data available, consisted of 1732 participants with 793 behavioural variables and 447 imaging variables (see Table S1 and S2 for a list).

2.3. CCA-ICA, split-half reliability, and permutation testing

To estimate modes of brain-behaviour-associations across participants, we used ICA with CCA as an intermediate step. The canonical variates from CCA represent linear combinations of the imaging variables that explain variance in linear combinations of the behavioural

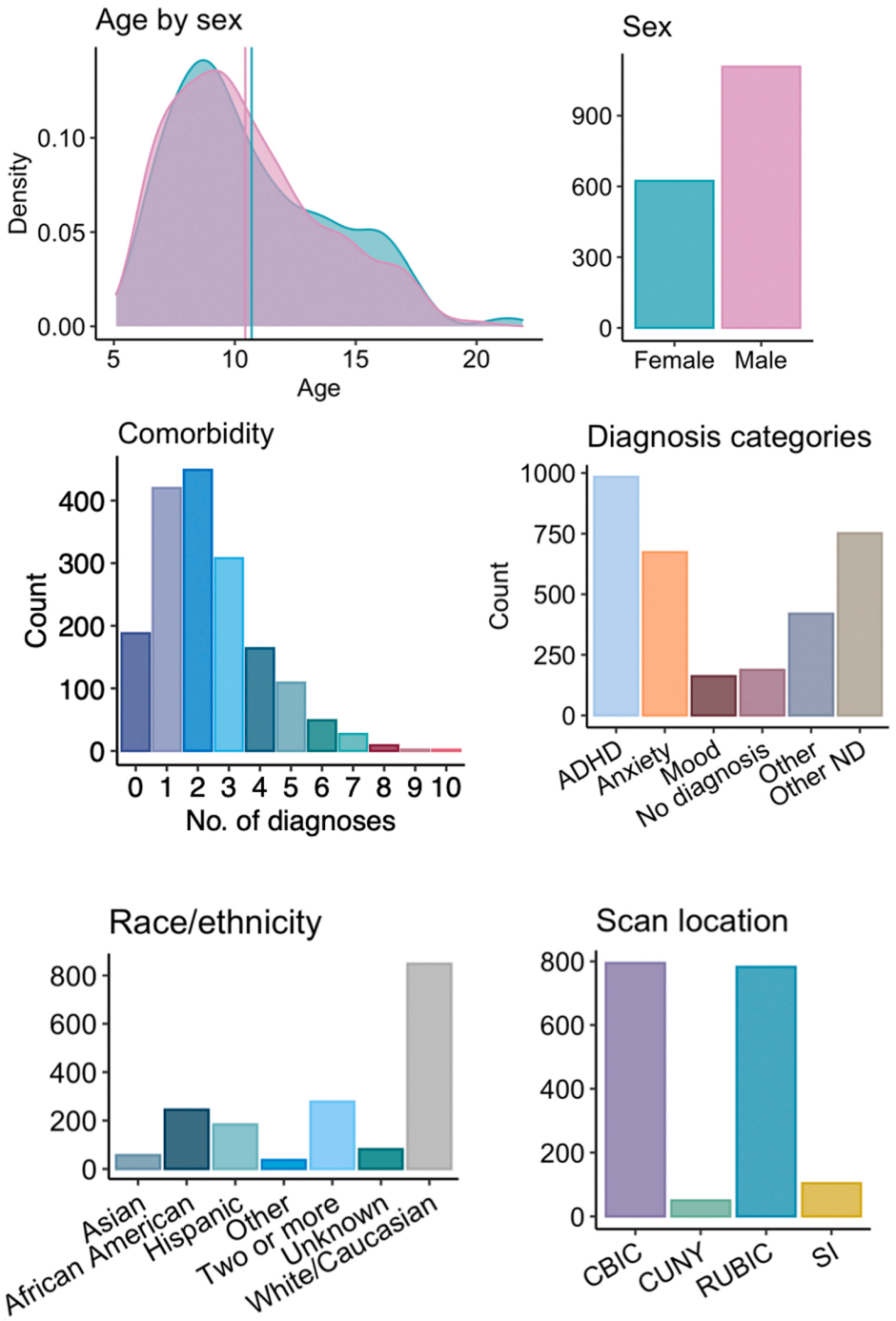

Fig. 1. Demographics and clinical characteristics of the sample. Distributions of age by sex, sex, comorbidity, diagnosis categories, racial/ethnic background, and scanner location.

variables across participants. To facilitate interpretation of the resulting orthogonal canonical variates, and following previous applications of CCA in population imaging (Alnæs et al., 2020; Miller et al., 2016), we submitted the CCA scores to ICA, using the fastICA algorithm (Hyvärinen and Oja, 2000). See Supplementary methods for more detail. To increase robustness, while at the same time avoiding rank deficiency and fitting to noise, we submitted both imaging and behavioural data to principal component analysis (PCA) before running CCA-ICA. All analyses were performed using MATLAB R2020b (Inc, 2020). As part of the analysis, we estimated the optimal dimensionality and decomposition for PCA and ICA and selected the dimensionality yielding the highest split-half reliability for the least reliable component (see Fig. S2 and S3). These tests revealed that results were robust to the choice of dimensionality. Next, the significance of the resulting CCA-ICA modes was tested using permutations (n = 1000), which inherently controls the family-wise error (FWE). To ensure that the initial CCA variates were significant (i.e. prior to ICA), these were also tested using permutations (n = 1000).

2.4. *Interpretation of CCA-ICA modes*

For plotting and interpretation of the resulting CCA-ICA modes, we

correlated the CCA-ICA participant weights (i.e. mode loadings) into the original de-confounded data. The resulting correlations reflect the strength with which each variable in the original data load onto the overarching pattern (akin to factor loadings), but do not inform us on the explicit strength of any bivariate relationships between individual variables. A lists of all variables, with correlations and CCA-ICA weights, are shown in Table S3 and S4.

2.5. Consistency across age, sex, racial/ethnic background, socioeconomic status, clinical diagnosis, and medication use

To assess the effect of age and sex on each mode, we plotted and regressed the mode loadings against age, age^2, and sex using linear models. We also reran the CCA-ICA with all behavioural phenotypes residualised with respect to sex. These results revealed similar patterns of covariation as the original analysis (correlations between the original and sex-adjusted results were $r = 0.94$ and $r = 0.80$ for mode 1 and mode 2, respectively). Similarly, we reran the correlations between mode loadings and original data controlling for age, to check the specific influence of age on each mode. These results revealed an almost identical pattern of covariation for mode 2 ($r = 0.98$), indicating that mode 1 ($r = 0.86$) captured most of the age-related variance. In effect, this age-residualised the data driving an age-invariant mode 2. See Fig. S5 for partial correlations between mode 2 and original data controlling for age.

Considering that factors related to inequality and socioeconomics differ between ethnic groups, these variables were not regressed out of the data. To examine whether the detected modes were generalisable across racial/ethnic background, we plotted the mode loadings by ethnic group (see Fig. S6). Similarly, we plotted the mode loadings by median-split of household income, as a proxy for socioeconomic status (SES; see Fig. S7). We also reran the correlations between mode loadings and original data controlling for household income. These results revealed unchanged patterns of covariation (correlations between the original and income-adjusted results were $r = 0.99$ for both modes), indicating that our results are consistent across socioeconomic levels. The correlation between household income and mode 2 weights was $r = 0.15$.

Based on clinical diagnostic information provided in the HBN sample, each participant was categorised based on their first given diagnosis, as either “ADHD”, “anxiety disorders”, “mood disorders”, “other disorders”, “other neurodevelopmental disorders” or “no diagnosis”. Mode loadings were then regressed against diagnosis, with pairwise comparisons estimated using the *emmeans* package in R and adjusted for multiple comparisons using Tukey. “No diagnosis” was used as a reference group. We also regressed mode loadings against number of diagnoses. All associations were adjusted for age, age^2, and sex.

As a cross check to investigate whether the dominance of ADHD in the sample influenced our findings, we then ran a leave-one-out-cross-validation of the CCA-ICA, excluding all those in the sample with an ADHD diagnosis. In this analysis, we decomposed the variables by multiplying them with the CCA-ICA weights estimated in the original analysis and then we correlated the mode loadings with the original data, as before. These results revealed similar patterns of covariation as the original analysis (the correlation between the original and leave-out-ADHD results was $r = 0.97$ for both modes), indicating that the dominance of ADHD did not unduly drive our findings. Finally, we also reran the correlations between mode loadings and original data controlling for medication use (yes/no; 288 participants reported yes). These results revealed unchanged patterns of covariation (correlations between the original and medication-adjusted results were $r = 0.99$ for both modes), indicating that our results are consistent across medication use.

2.6. Out-of-sample validation

For the validation sample, we accessed brain MRI, cognitive, and clinical data from the Philadelphia Neurodevelopmental Cohort (PNC), a large community-based study of brain development in youths aged 8–21 (Satterthwaite et al., 2016). As a sub-sample of the larger study, 1445 participants have undergone MRI. Participants were recruited from a larger genetic study at the Children’s Hospital of Philadelphia, stratified by sex, age, and ethnicity. After pre-processing and quality control, the final sample consisted of 1253 participants (681 females). Age distribution is provided in Fig. S8.

The MRI data was processed using the same analysis pipeline as described above for HBN. Clinical variables included 129 symptom scores decomposed into 7 components using ICA, as reported previously (Alnaes et al., 2018): Attention/ADHD, anxiety, conduct disorder, depression, psychosis prodrome, mania, and obsessive-compulsive disorder (Hettwer et al., 2022). These clinical symptom components reflect increased presence of symptoms. In addition, we included a general symptom burden measure (mean clinical ICA-score). As cognitive measures, we included a general cognitive ability factor (gF, first principal component from a PCA across 12 cognitive tests) (Alnaes et al., 2018) and a social cognitive score (the sum of the Penn Emotion Identification Test and Penn Emotion Differentiation Test) (Moore et al., 2015), in addition to a normative deviation score for cognitive abilities (Kjelkenes et al., 2022), which reflects the deviation of each participant’s cognitive ability relative to same-aged peers.

To assess whether the brain-side of the CCA-ICA results were replicable in the validation sample, we decomposed the PNC MRI variables by multiplying them with the imaging CCA-ICA weights estimated in HBN. To test whether the resulting MRI spatial maps in PNC overlapped with those of HBN, we correlated them and tested the significance of these correlations using spin permutations (Vos de Wael et al., 2020; Alexander-Bloch et al., 2018). Then, to investigate whether the brain-behaviour pattern was generalisable to the validation sample, we tested whether the detected brain pattern in PNC could predict scores on clinical and cognitive measures. To do this, we correlated the brain loadings with clinical and cognitive scores in the PNC sample. These scores were not overlapping with clinical and cognitive scores in HBN, so they could not be directly compared. However, if the clinical and cognitive variables in each sample are ecologically valid, they should yield comparable associations with the detected brain pattern, if the detected pattern is indeed generalisable. To assess the reliability of the associations between derived brain loadings and clinical and cognitive variables in PNC, we performed 1000 bootstraps using resampling with replacement. For each bootstrap iteration we decomposed the MRI variables and correlated the derived brain loadings with the clinical and cognitive measures. The resulting bootstrap distribution was used to calculate the 95 % confidence intervals for the out-of-sample brain scores vs cognitive-clinical correlations.

3. Results

3.1. Modes of covariation

By joint multivariate modelling using CCA-ICA, we aimed to delineate linked dimensions (i.e. modes of covariation) between brain structure and clinical, cognitive, and socio-environmental variables in a clinical sample of youth. This analysis identified two such modes of brain-behaviour covariation (both $r = 0.92$, $p_{corr} = .005$ and $p_{corr} = .006$ for mode 1 and mode 2, respectively). In the initial CCA (i.e. prior to ICA), $p_{corr} = .001$ for the two first variates. Each mode of brain-behaviour covariation represents a distinct pattern that relates a weighted set of cognitive, clinical, and socio-environmental factors to a weighted set of brain structures. As shown in Fig. 2A, mode 1 captured a pattern of associations linked to physical and cognitive maturation. The most heavily weighted variables included age, height, weight, pubertal development, and academic performance such as numerical operations, spelling, and word reading. Higher scores on these measures were linked to less parental supervision at home, less need for help with homework,

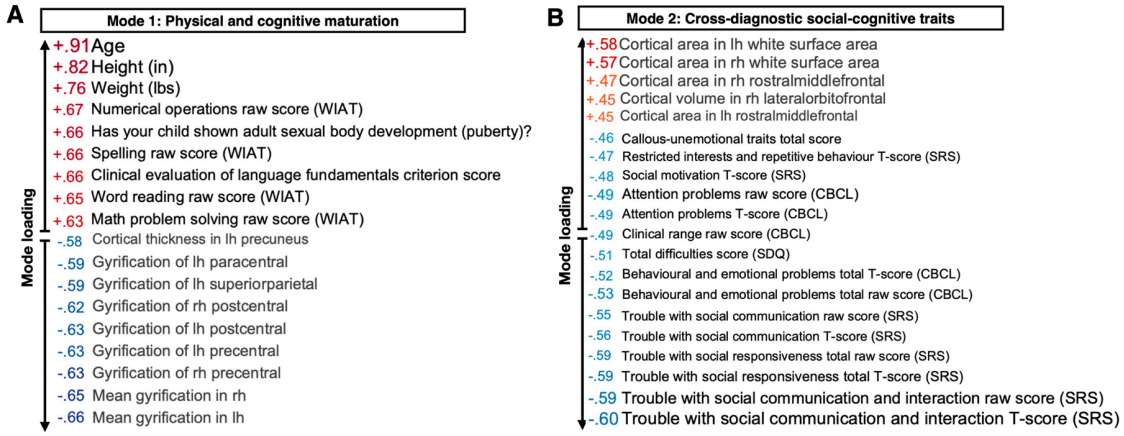

Fig. 2. Multivariate pattern of brain-behaviour associations across diagnostic boundaries in youth. **Left:** Mode 1 captures a pattern linking age, physical, and cognitive maturation with lower cortical thickness and gyrification. **Right:** Mode 2 captures a pattern linking trouble with social communication, cognitive ability, and symptoms of psychopathology with lower white matter surface area and gyrification. The values represent correlations between original data values and participant CCA-ICA weights (i.e. mode loadings). Depicted here are the variables with the strongest associations with each mode. In; inches. Lbs; pounds. WIAT; Wechsler individual achievement test. Lh; left hemisphere. Rh; right hemisphere. CBCL; child behavior checklist. SDQ; strengths and difficulties questionnaire. SRS; social responsiveness scale.

lower prevalence of depressive symptoms, and being able to stay seated in the classroom. In relation to the brain, this mode was associated with lower cortical thickness and gyrification, specifically in the global gyrification index (GI), precentral, postcentral, and paracentral GI, as well as precuneus, superiorparietal, and mean cortical thickness.

Mode 2 captured a pattern of clinical and cognitive scores, independent of age. Specifically, mode 2 linked language skills, academic performance, and trouble with social communication to distinct patterns of brain structure (see Fig. 2B). Trouble with social communication and social cognition overall was associated with worse phonological processing and other indications of language fundamentals, worse academic performance, and having an individualised education plan. These measures were further linked to callous-unemotional traits, lower social status, and higher prevalence of psychological difficulties such as attention problems, externalisation, internalisation, and hyperactivity. This pattern of associations was linked to several brain features, such as lower global white matter surface area, rostral middle frontal cortical area, lateral orbitofrontal cortical volume, and regional as well as mean cortical gyrification. See Fig. S9 for loadings of all variables included in the analysis.

To understand the degree to which these linked dimensions were disorder-general or disorder-specific, we then investigated the extent to which diagnostic categories explained individual differences in loading on each mode. Fig. 3 shows loading on mode 2 by diagnostic category and by number of diagnoses (see Fig. S10 for loading on mode 1). Linear models (see Table 1, S5, S6, and S7) revealed that participants diagnosed

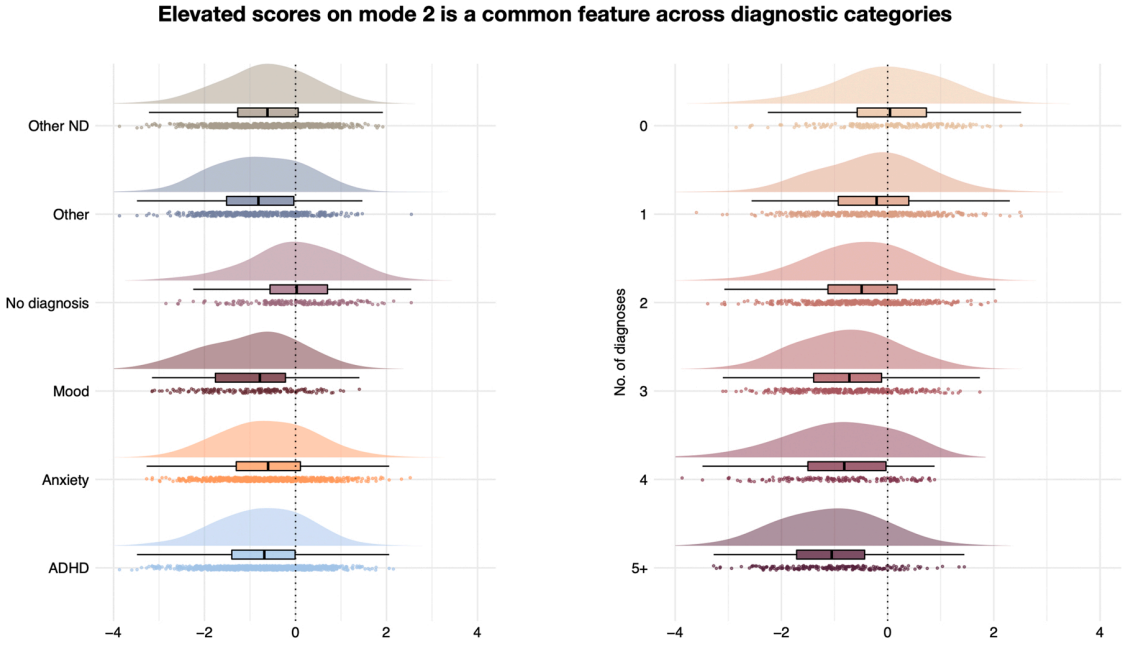

Fig. 3. A larger, more negative score on mode 2 (linking social skills, cognitive ability, and psychopathology to brain structure) was a common feature across all diagnostic boundaries. **Left:** All diagnostic categories had a stronger, more negative loading on mode 2 compared to having no diagnosis. **Right:** Stronger, more negative loading on mode 2 by increasing number of diagnoses (comorbidities). Box plot notches exhibit 95 % confidence intervals for comparing medians. Centred around no diagnosis median. ADHD; attention-deficit hyperactivity disorders. Other ND; other neurodevelopmental disorders.

Table 1
Pairwise comparisons of associations with each mode between no diagnosis and each diagnostic category. Age, age^2, and sex are included as covariates.

Comparison	Beta	SE	df	LL	UL	t-value	corr p
Mode 1							
ADHD	0.03	0.04	1719	-0.08	0.13	0.73	0.978
Anxiety	0.01	0.04	1719	-0.11	0.13	0.28	1.000
Mood	0.27	0.06	1719	0.09	0.46	4.22	3.7×10^{-4}
Other	< 0.01	0.06	1719	-0.18	0.17	-0.06	1.00
Other ND	0.06	0.04	1719	-0.05	0.17	1.58	0.611
Mode 2							
ADHD	-0.68	0.08	1719	-0.91	-0.46	-8.64	3.7×10^{-12}
Anxiety	-0.24	0.09	1719	-0.51	0.02	-2.66	0.084
Mood	-0.74	0.14	1719	-1.15	-0.33	-5.15	4.3×10^{-6}
Other	-0.51	0.14	1719	-0.90	-0.12	-3.71	0.003
Other ND	-0.57	0.09	1719	-0.81	-0.32	-6.59	8.7×10^{-10}

Note. ADHD; attention-deficit hyperactivity disorders. ND; neurodevelopmental disorders. SE; standard error. df; degrees of freedom. LL; lower confidence level (2.5 %). UL; upper confidence level (97.5 %). corr p; p-value adjusted with Tukey.

with mood disorders showed a higher loading on mode 1, while all diagnostic categories, except anxiety disorders, were associated with more negative loading on mode 2 compared to participants without a diagnosis. Both mode 1 and mode 2 exhibited a significant linear association with the number of diagnoses (see Table S8 and S9). This was true when including "no diagnosis" in the model or not, suggesting that this effect was not driven by case-control effects.

3.2. Out-of-sample validation

As a final step, we tested the replicability and generalisability of our findings using an independent sample. Using the brain pattern derived from the HBN sample, we estimated feature weights (i.e. loadings) across MRI variables in the PNC sample. Comparing these loadings, we found strong positive correlations between the two samples ($r = 0.95$, $p_{corr} < .001$ and $r = 0.71$, $p_{corr} < .001$ for mode 1 and mode 2, respectively; see Fig. S11 for null distributions of the spin permutation test). As shown in Fig. S12 and S13, the covariation structure across MRI variables in PNC highly resembled HBN. Next, to test the generalisability and predictive ability of the brain patterns to clinical and cognitive measures, we estimated correlations between the derived brain scores in PNC with cognitive and clinical variables. While the measured clinical and cognitive constructs were similar between the two samples, they were not assessed using identical instruments. Thus, this out-of-sample validation also constitutes a test of the external validity of the brain-behaviour relationship. This analysis revealed that a larger, more negative mode 2 brain loading was linked to greater negative deviation from a normative cognitive trajectory, lower cognitive abilities, higher average symptom burden, as well as higher symptoms of anxiety and conduct disorder (see Fig. 4). Mode 2 was largely age invariant, however, to further confirm the age-independence of mode 2, the scores were residualised with respect to age in this plot. Mode 1 exhibited positive associations with age and cognitive abilities, as well as higher average symptom burden (see Fig. S14).

4. Discussion

In this study we leveraged the HBN sample, a clinical youth cohort aged 5–21, to delineate dimensions of brain-behaviour associations across diagnostic boundaries in youth. We identified two modes of brain-behaviour covariation, linking maturation, cognitive ability, social skills, and symptoms of psychopathology to individual differences in brain structure. The dimension linking cognitive ability, social skills, and symptoms of psychopathology to brain structure was a common feature across all diagnostic boundaries, suggesting a disorder-general effect. We also demonstrated the generalisability and predictive ability of these patterns in an independent population-based sample with a similar age range. Together, these findings suggest that brain-behaviour associations in youth are broad and transdiagnostic, implicating factors such as cognitive ability and social skills and scaling with the number of comorbid illnesses.

The first mode linked lower cortical thickness and gyrification with age and measures of physical and cognitive maturation, reflecting age-related improvements in school performance, pubertal development, higher height, and weight. This mode replicates previous studies in youth showing lower cortical thickness (Shaw et al., 2008; Mills et al., 2016; Tamnes et al., 2010) and gyrification (Raznahan et al., 2011; Su et al., 2013) with increasing age, as well as cognitive maturation (Chung et al., 2017). Moreover, our results align with a previous multivariate investigation in a longitudinal sample of adolescents (Modabbernia et al., 2021a), identifying the strongest brain-behaviour associations to be between measures of brain structure and sex, age, and indices of maturation. This emphasises common maturational factors as the most important influences on neurodevelopment, also when environmental,

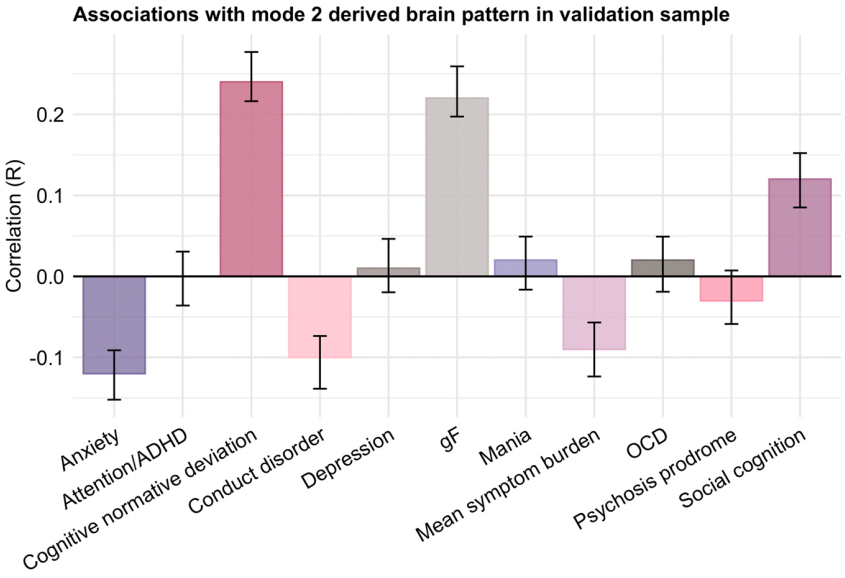

Fig. 4. Mode 2 derived brain loadings in PNC correlate with comparable clinical and cognitive measures. A larger, more negative score on mode 2 is correlated with lower cognitive ability and negative deviations from normative cognitive development. A negative cognitive normative deviation indicates poorer cognitive development than expected. Error bars represent bootstrapped 95 % confidence intervals for correlations across 1000 bootstrap-decompositions of the PNC imaging data. ADHD; attention-deficit hyperactivity disorder. OCD; obsessive compulsive disorder. gF; general cognitive ability.

demographical, and psychosocial influences were considered.

The second mode captured a pattern of socio-cognitive difficulties associated with lower cortical volume, surface area, and gyrification. Specifically, this pattern reflected difficulties with communicating and relating to peers, worse language development and school performance, and emerging psychological difficulties. Such a "positive-negative" dimension across behavioural, clinical, and socio-environmental factors has previously been linked to individual differences in brain morphology and connectivity in population-based samples (Smith et al., 2015; Alnæs et al., 2020; Modabbernia et al., 2021b). The current results extend these findings by demonstrating their relevance for characterising psychopathology in youth that already have a psychiatric diagnosis. Indeed, we established that the current pattern was detectable also in an independent population-based sample. This overlap between clinical and non-clinical populations lend support to the conceptualisation of psychopathology as existing on a continuum, such as the p-factor framework (Caspi and Moffitt, 2018). Importantly, the pattern we identified was common across all diagnostic boundaries, indicating a disorder-general or shared pattern. Having a higher number of diagnoses (i.e. comorbidities) was also associated with larger deviations (i.e. larger, more negative loading) on mode 2. This is in line with comorbidity as a prevalent feature of mental illness (Plana-Ripoll et al., 2019), as well as the finding that transdiagnostic symptom burden (i.e. the p-factor) is more predictive of clinical life trajectories than any specific diagnosis (Caspi et al., 2020, 2014). This has implications for prevention and interventions targeting risk for mental illness in youth, as well as the understanding of psychopathology aetiology more broadly.

Previous work on shared brain structural abnormalities across diagnostic boundaries in adults found one latent factor to explain abnormalities associated with major depression, bipolar disorder, schizophrenia, and OCD, while abnormalities in ADHD and autism spectrum disorder (ASD) were largely independent (Opel et al., 2020). Contrary to this, we found a great degree of overlap in brain-behaviour associations across all disorders. In the current work, the brain associations across disorders were constrained by their link to the behaviour-associations, which may explain the different results. Whether neurodevelopmental disorders belong in the general psychopathology domain or rather represent separate entities remains a topic of discussion (Ronald, 2019). Our findings suggest that in terms of brain-behaviour associations, ADHD and ASD belong in the same terrain as other psychiatric disorders.

Cortical surface area was among the highest loading brain measures on mode 2, the dimension linked to cognitive ability, social skills, and psychopathology. Postnatal surface area expansion has been proposed to reflect local cellular events, such as intracortical myelination, gliogenesis, synaptogenesis and dendritic arborization (Hill et al., 2010). In typically developing children, surface area increases until late childhood or early adolescence (Amlien et al., 2016). As such, lower surface area may reflect disadvantageous or delayed brain development. Indeed, smaller surface area has been linked to poorer cognition, poorer physical development, and poorer social environment in children aged 9–10 relative to same-aged peers (Modabbernia et al., 2021b). Given that surface area was adjusted for eTIV in our analyses, the high loading of this brain feature likely reflect cortical folding, the only plausible avenue for expanding cortical surface area without a corresponding expansion of intracranial volume (Mota and Herculano-Houzel, 2015). Indeed, both global and regional cortical gyrification were also among the highest loading brain features on mode 2.

Gyrification typically decreases from middle childhood until young adulthood (Raznahan et al., 2011), and we replicated this age-related gyrification pattern in mode 1. Mode 2 was, however, only weakly associated with age, and the pattern of lower gyrification here was linked to individual differences in clinical and cognitive measures. Common age-related effects appear to be captured by mode 1, as shown by the fact that raw scores and t scores on cognitive tests exhibit overlapping loading on mode 2. Moreover, the pattern of variable loading in mode 2 when controlling for age was largely overlapping with the original uncorrected analysis, further supporting this interpretation. As such, the pattern of associations in mode 2 is to a large extent age invariant and represent other mechanisms than merely the effect of age.

Reduced cortical folding in individuals with socio-cognitive difficulties is in line with previous work relating lower gyrification to neurodevelopmental diagnoses such as ADHD (Wolosin et al., 2009), ASD (Bos et al., 2015), intellectual disability (Zhang et al., 2010), and dyslexia (Casanova et al., 2004). This association may thus represent an important neural correlate for social and neurocognitive difficulties. Indeed, our validation of the mode 2 brain pattern in an independent population-based sample revealed a robust association with deviations from normative cognitive development. These results suggests that cognitive problems represent a relevant characteristic of mental illness across diagnostic boundaries, which is compatible with previous findings identifying cognition as a common risk factor for psychopathology and a core characteristic of general vulnerability for psychopathology (Abramovitch et al., 2021; Caspi et al., 2014; Michelini et al., 2019). Interventions aimed at improving mental health in youth may thus benefit from targeting cognitive development and the environments supporting it, such as schools and education. In line with previous findings linking SES to vulnerability for mental illness (Reiss, 2013), mode 2 was associated with SES. However, the correlation was moderate, suggesting that brain-linked vulnerability cannot be simply explained as SES-driven individual differences.

Other studies have reported shared brain connectivity patterns across anxiety, irritability, and ADHD in other clinical samples of youth (Linke et al., 2021). While substantial evidence now points towards cross-diagnostic brain deviations in psychopathology (Goodkind et al., 2015; Sha et al., 2019), this does not rule out disorder-specific patterns, and a full account of the brain basis of mental illness require mapping of both (Linke et al., 2021; Buckholtz and Meyer-Lindenberg, 2012). Mood disorders predicted mode 1 in addition to mode 2, unlike the other diagnostic categories which were only linked to mode 2. This is likely driven by the fact that individuals with a mood disorder were older than the rest of the sample. Having a higher number of diagnoses was also associated with higher loading on mode 1, likely reflecting the increased prevalence of diagnoses with increasing age (Caspi et al., 2020).

Some limitations should be noted. Acquiring high-quality neuroimaging data in youth and clinical samples is challenging, especially in clinical cohorts. Here we utilised the MRIQC classifier to exclude participants with insufficient image quality and excluded any remining extreme data points from analysis. Both samples applied cross-sectional designs, while longitudinal studies are required to conclude whether the observed age-related individual differences reflect within-person developmental trajectories. Multiple measurements may also allow for determining the dynamic interplay between environmental factors, mental health symptoms, and brain changes, thereby illuminating whether brain changes precede or is a consequence of mental health symptoms (Muetzel et al., 2017). The current sample consisted of largely children with a clinical diagnosis. Although evidence suggests substantial overlap across diagnostic boundaries, we do not know whether those individuals who develop mental illness early in life represent a qualitatively different group in terms of aetiology compared to those developing mental illness during adolescence and early adulthood. Evidence suggests that age-of-onset is an important aspect of the p-factor, which is more predictive of clinical life trajectories than any specific diagnosis (Caspi et al., 2020, 2014). The identified brain-behaviour patterns were detectable in an independent sample, which further supports the generalisability of our findings and is a strength of the current study.

5. Conclusions

In this study, we delineated dimensions of brain-behaviour associations across diagnostic boundaries in youth. In addition to expected patterns of maturation, we found that lower cognitive ability, poor

social skills, and symptoms of psychopathology are linked to individual differences in brain structure, and that this is a common feature across diagnostic boundaries. These findings were detectable in an independent sample, supporting their generalisability and predictive ability. In line with the p-factor framework, this suggests that broad and transdiagnostic effects are the most potent patterns of brain-behaviour associations. This emphasises the importance of transdiagnostic approaches in the identification of shared and distinct patterns relevant for psychopathology, a critical step towards more informed models of psychopathology.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: OAA is a consultant to HealthLytix and received speaker's honoraria from Lundbeck. All other authors report no biomedical financial interests or potential conflicts of interest.

Data Availability

The data that forms the basis of this work were obtained from the open access Healthy Brain Network (https://healthybrainnetwork.org/) and The Philadelphia Neurodevelopmental Cohort resources (https://www.med.upenn.edu/bbl/philadelphianeurodevelopmentalcohort.html). The code used in the study is available in a public repository (Open Science Framework) (https://osf.io/cjerd/).

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dcn.2023.101219.

References

Abramovitch, A., Short, T., Schweiger, A., 2021. The C Factor: cognitive dysfunction as a transdiagnostic dimension in psychopathology. Clin. Psychol. Rev. 86, 102007.
Alexander, L.M., et al., 2017. An open resource for transdiagnostic research in pediatric mental health and learning disorders. Sci. Data 4 (1), 1–26.
Alexander-Bloch, A.F., et al., 2018. On testing for spatial correspondence between maps of human brain structure and function. Neuroimage 178, 540–551.
Alnaes, D., et al., 2018. Association of heritable cognitive ability and psychopathology with white matter properties in children and adolescents. JAMA Psychiatry 75 (3), 287–295.
Alnæs, D., et al., 2020. Patterns of sociocognitive stratification and perinatal risk in the child brain. Proc. Natl. Acad. Sci., 117(22), pp. 12419–12427.
Amlien, I.K., et al., 2016. Organizing principles of human cortical development—thickness and area from 4 to 30 years: insights from comparative primate neuroanatomy. Cereb. Cortex 26 (1), 257–267.
Ball, G., et al., 2018. Multimodal structural neuroimaging markers of brain development and ADHD symptoms. Am. J. Psychiatry 176 (1), 57–66.
Billot, B., et al., 2020. Automated segmentation of the hypothalamus and associated subunits in brain MRI. NeuroImage 223, 117287.
Bos, D.J., et al., 2015. Reduced gyrification is related to reduced interhemispheric connectivity in autism spectrum disorders. J. Am. Acad. Child Adolesc. Psychiatry 54 (8), 668–676.
Buckholtz, J.W., Meyer-Lindenberg, A., 2012. Psychopathology and the human connectome: toward a transdiagnostic model of risk for mental illness. Neuron 74 (6), 990–1004.
Casanova, M.F., et al., 2004. Reduced brain size and gyrification in the brains of dyslexic patients. J. Child Neurol. 19 (4), 275–281.
Caspi, A., et al., 2014. The p factor: one general psychopathology factor in the structure of psychiatric disorders? Clin. Psychol. Sci. 2 (2), 119–137.
Caspi, A., et al., 2020. Longitudinal assessment of mental health disorders and comorbidities across 4 decades among participants in the dunedin birth cohort study. JAMA Netw. Open 3 (4) e203221-e203221.
Caspi, A., Moffitt, T.E., 2018. All for one and one for all: mental disorders in one dimension. Am. J. Psychiatry 175 (9), 831–844.
Chaytor, N., Schmitter-Edgecombe, M., 2003. The ecological validity of neuropsychological tests: a review of the literature on everyday cognitive skills. Neuropsychol. Rev. 13 (4), 181–197.
Chung, Y.S., Hyatt, C.J., Stevens, M.C., 2017. Adolescent maturation of the relationship between cortical gyrification and cognitive ability. NeuroImage 158, 319–331.
Esteban, O., et al., 2017. MRIQC: advancing the automatic prediction of image quality in MRI from unseen sites. PLoS One 12 (9), e0184661.
Fischl, B., 2012. FreeSurfer. NeuroImage 62 (2), 774–781.
Goodkind, M., et al., 2015. Identification of a common neurobiological substrate for mental illness. JAMA Psychiatry 72 (4), 305–315.
Hettwer, M.D., et al., 2022. Coordinated cortical thickness alterations across six neurodevelopmental and psychiatric disorders. Nat. Commun. 13 (1), 6851.
Hill, J., et al., 2010. Similar patterns of cortical expansion during human development and evolution. Proceedings of the National Academy of Sciences, 107(29), pp. 13135–13140.
Hyvärinen, A., Oja, E., 2000. Independent component analysis: algorithms and applications. Neural Netw. 13 (4–5), 411-30.
Iglesias, J.E., et al., 2015a. A computational atlas of the hippocampal formation using ex vivo, ultra-high resolution MRI: Application to adaptive segmentation of in vivo MRI. NeuroImage 115, 117–137.
Iglesias, J.E., et al., 2015b. Bayesian segmentation of brainstem structures in MRI. NeuroImage 113, 184–195.
Iglesias, J.E., et al., 2018. A probabilistic atlas of the human thalamic nuclei combining ex vivo MRI and histology. Neuroimage 183, 314–326.
Inc, T.M., MATLAB. 2020: Natick, Massachusetts.
Kessler, R.C., et al., 2007. Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. World Psychiatry 6 (3), 168.
Kjelkenes, R., et al., 2022. Mapping normative trajectories of cognitive function and its relation to psychopathology symptoms and genetic risk in youth. Biol. Psychiatry: Global Open Sci.
Lahey, B.B., et al., 2011. Higher-order genetic and environmental structure of prevalent forms of child and adolescent psychopathology. Arch. Gen. Psychiatry 68 (2), 181–189.
Linke, J.O., et al., 2021. Shared and anxiety-specific pediatric psychopathology dimensions manifest distributed neural correlates. Biol. Psychiatry 89 (6), 579–587.
Lynch, S.J., et al., 2021. A systematic review of transdiagnostic risk and protective factors for general and specific psychopathology in young people. Clin. Psychol. Rev. 87, 102036.
Michelini, G., et al., 2019. Delineating and validating higher-order dimensions of psychopathology in the Adolescent Brain Cognitive Development (ABCD) study. Translational. Psychiatry 9 (1), 261.
Miller, K.L., et al., 2016. Multimodal population brain imaging in the UK Biobank prospective epidemiological study. Nat. Neurosci. 19 (11), 1523–1536.
Mills, K.L., et al., 2016. Structural brain development between childhood and adulthood: Convergence across four longitudinal samples. Neuroimage 141, 273–281.
Modabbernia, A., et al., 2021a. Linked patterns of biological and environmental covariation with brain structure in adolescence: a population-based longitudinal study. Mol. Psychiatry 26 (9), 4905–4918.
Modabbernia, A., et al., 2021b. Multivariate patterns of brain-behavior-environment associations in the adolescent brain and cognitive development study. Biol. Psychiatry 89 (5), 510–520.
Moore, T.M., et al., 2015. Psychometric properties of the Penn computerized neurocognitive battery. Neuropsychology 29 (2), 235.
Mota, B., Herculano-Houzel, S., 2015. Cortical folding scales universally with surface area and thickness, not number of neurons. Science 349 (6243), 74–77.
Muetzel, R.L., et al., 2017. Tracking brain development and dimensional psychiatric symptoms in children: a longitudinal population-based neuroimaging study. Am. J. Psychiatry 175 (1), 54–62.
Opel, N., et al., 2020. Cross-disorder analysis of brain structural abnormalities in six major psychiatric disorders: a secondary analysis of mega- and meta-analytical findings from the ENIGMA consortium. Biol. Psychiatry 88 (9), 678–686.

Parkes, L., et al., 2021. Transdiagnostic dimensions of psychopathology explain individuals' unique deviations from normative neurodevelopment in brain structure. Transl. Psychiatry 11 (1), 232.
Pettersson, E., Larsson, H., Lichtenstein, P., 2016. Common psychiatric disorders share the same genetic origin: a multivariate sibling study of the Swedish population. Mol. Psychiatry 21 (5), 717–721.
Plana-Ripoll, O., et al., 2019. Exploring comorbidity within mental disorders among a Danish National Population. JAMA Psychiatry 76 (3), 259–270.
Raznahan, A., et al., 2011. How does your cortex grow? J. Neurosci. 31 (19), 7174.
Reiss, F., 2013. Socioeconomic inequalities and mental health problems in children and adolescents: a systematic review. Soc. Sci. Med. 90, 24–31.
Roelfs, D., et al., 2021. Phenotypically independent profiles relevant to mental health are genetically correlated. Transl. Psychiatry 11 (1), 202.
Ronald, A., 2019. Editorial: The psychopathology p factor: will it revolutionise the science and practice of child and adolescent psychiatry? J. Child Psychol. Psychiatry 60 (5), 497–499.
Satterthwaite, T.D., et al., 2016. The Philadelphia Neurodevelopmental Cohort: A publicly available resource for the study of normal and abnormal brain development in youth. Neuroimage, 124(Pt B), pp. 1115–1119.
Saygin, Z.M., et al., 2017. High-resolution magnetic resonance imaging reveals nuclei of the human amygdala: manual segmentation to automatic atlas. NeuroImage 155, 370–382.
Sha, Z., et al., 2019. Common dysfunction of large-scale neurocognitive networks across psychiatric disorders. Biol. Psychiatry 85 (5), 379–388.
Shaw, P., et al., 2008. Neurodevelopmental trajectories of the human cerebral cortex. J. Neurosci. 28 (14), 3586.
Smith, S.M., et al., 2015. A positive-negative mode of population covariation links brain connectivity, demographics and behavior. Nat. Neurosci. 18 (11), 1565–1567.
Su, S., et al., 2013. Geometric computation of human gyrification indexes from magnetic resonance images. Hum. Brain Mapp. 34 (5), 1230–1244.
Tamnes, C.K., et al., 2010. Brain maturation in adolescence and young adulthood: regional age-related changes in cortical thickness and white matter volume and microstructure. Cereb. Cortex 20 (3), 534–548.
Vos de Wael, R., et al., 2020. BrainSpace: a toolbox for the analysis of macroscale gradients in neuroimaging and connectomics datasets. Commun. Biol. 3 (1), 103.
Winkler, A.M., et al., 2014. Permutation inference for the general linear model. NeuroImage 92, 381–397.
Wolosin, S.M., et al., 2009. Abnormal cerebral cortex structure in children with ADHD. Hum. Brain Mapp. 30 (1), 175–184.
Zhang, Y., et al., 2010. Reduced cortical folding in mental retardation. Am. J. Neuroradiol. 31 (6), 1063.

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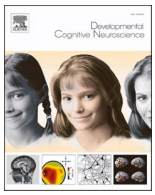

Delineating disorder-general and disorder-specific dimensions of psychopathology from functional brain networks in a developmental clinical sample

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ABSTRACT

The interplay between functional brain network maturation and psychopathology during development remains elusive. To establish the structure of psychopathology and its neurobiological mechanisms, mapping of both shared and unique functional connectivity patterns across developmental clinical populations is needed. We investigated shared associations between resting-state functional connectivity and psychopathology in children and adolescents aged 5–21 (n = 1689). Specifically, we used partial least squares (PLS) to identify latent variables (LV) between connectivity and both symptom scores and diagnostic information. We also investigated associations between connectivity and each diagnosis specifically, controlling for other diagnosis categories. PLS identified five significant LVs between connectivity and symptoms, mapping onto the psychopathology hierarchy. The first LV resembled a general psychopathology factor, followed by dimensions of internalising- externalising, neurodevelopment, somatic complaints, and thought problems. Another PLS with diagnostic data revealed one significant LV, resembling a cross-diagnostic case-control pattern. The diagnosis-specific PLS identified a unique connectivity pattern for autism spectrum disorder (ASD). All LVs were associated with distinct patterns of functional connectivity. These dimensions largely replicated in an independent sample (n = 420) from the same dataset, as well as to an independent cohort (n = 3504). This suggests that covariance in developmental functional brain networks supports transdiagnostic dimensions of psychopathology.

1. Introduction

Establishing the structure of psychopathology and its underlying neurobiological mechanisms is a critical step towards personalised approaches in mental health research and care. The high rate of comorbidity between diagnoses challenges the utility of traditional case-control designs and motivates novel strategies for clinical phenotyping such as transdiagnostic assessment of psychopathology dimensions (Caspi et al., 2014; Insel et al., 2010). Existing diagnostic categories do not map onto disorder-specific neurobiological substrates (Insel and Cuthbert, 2015), and many of the detected abnormalities in both genetics (Hindley et al., 2022; Lahey et al., 2011; Pettersson et al., 2016; Roelfs et al., 2021), brain structure (Goodkind et al., 2015; Opel et al., 2020a) and brain function (Elliott et al., 2018; McTeague et al., 2017; McTeague et al., 2020; Sha et al., 2019) are shared across disorders. Investigation into the neurobiological substrates of distinct symptom

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dimensions may therefore elucidate the brain-based underpinnings of mental disorders.

Childhood and adolescence are characterised by large scale reorganisation and maturation of the brain and its functional networks (Paus et al., 2008; Power et al., 2010). Given that mental disorders often first manifest during this time (Caspi et al., 2020; Kessler et al., 2007), aberrant functional network development may represent a key aetiological component in mental disorders (Casey et al., 2014; Paus et al., 2008). Indeed, while sensory and motor regions and their associated functional networks typically are fully developed by late childhood, the association cortex, and implicated functional networks such as the default mode network (DMN), take longer to mature. This might leave these brain circuits vulnerable to emerging psychopathology during neurodevelopment (Sydnor et al., 2021). To identify biologically informed dimensions of psychopathology, investigating associations between functional brain networks and psychopathology during childhood and adolescence is imperative.

Psychopathology is increasingly conceptualised as a hierarchical structure (Caspi et al., 2014; Kotov et al., 2017; Lahey et al., 2017). This hierarchy consists of a general psychopathology factor as the highest order, reflecting a general vulnerability to psychopathology, followed by increasingly narrow dimensions, such as internalising and externalising. These reflect anxious and depressive symptoms, and aggressive, rule-breaking, and hyperactive symptoms, respectively. A neurodevelopmental factor is also often included to reflect autistic-like traits and symptoms of attention deficit hyperactivity disorder (ADHD). For example, recent work in the Adolescent Brain Cognitive Development (ABCD) cohort (Casey et al., 2018) derived five dimensions of psychopathology (i.e. internalising, externalising, neurodevelopmental, detachment, and somatoform) using exploratory factor analysis on symptom data (Michelini et al., 2019). Similar psychopathology dimensions have been derived from both symptom data (Karcher et al., 2021) and diagnostic data (Lees et al., 2021) and then associated with patterns of functional connectivity obtained from resting-state functional magnetic resonance imaging (rs-fMRI). However, these studies derived dimensions of psychopathology from symptom data or diagnostic information in isolation, and only afterwards associated them with functional connectivity. To identify brain-based dimensions of psychopathology, the functional brain networks should inform the estimation of psychopathology dimensions per se.

Doing exactly this, studies have identified symptom dimensions by finding their maximal correlation with functional connectivity in youth aged 8–22 (Xia et al., 2018) and preadolescents aged 9–11 (i.e., the ABCD cohort) (Kebets et al., 2023). In youth, dimensions of mood, psychosis, fear, and externalisation symptoms exhibited both unique and a shared pattern of connectivity. In ABCD, dimensions derived from structural and functional brain patterns simultaneously resembled a general psychopathology factor along with internalising-externalising, neurodevelopmental, somatoform, and detachment dimensions. Although this work is promising with respect to identifying biologically informed dimensions of psychopathology, the investigation of mental health symptoms in population-based studies may not generalise to clinical populations (Vanes and Dolan, 2021). While investigation in young, representative cohorts is essential to understand putative developmental mechanisms relevant for psychopathological vulnerability, it is equally important to map the relevance of these findings to individuals already diagnosed with a mental disorder. Mapping of disorder-general and disorder-specific patterns in clinical populations is needed to elucidate the underlying neurobiological mechanisms of psychopathology.

Patterns of connectivity related to symptoms of anxiety, irritability, and ADHD were replicated across two independent clinical samples of children and adolescents (Linke et al., 2021). Specifically, this study identified one dimension consisting of all three domains, while the second dimension captured shared aspects of irritability and ADHD, and the third was specific to anxiety. This indicates clinically relevant disorder-general (i.e., shared across disorders) and disorder-specific effects in functional networks of children and adolescents. Moreover, it points to the possibility of decomposing irritability, a symptom shared between anxiety and ADHD, into disorder-specific and common components based on patterns of brain connectivity. However, this study did not investigate connectivity patterns related to broad transdiagnostic symptom dimensions but maintained a focus limited to anxiety, irritability, and attention problems. Moreover, the degree of overlap between functional networks linked to symptom dimensions and those related to diagnosis remain to be determined.

In the current study, we aimed to investigate dimensions linking functional connectivity and psychopathology in a sample of children and adolescents where the majority had at least one diagnosed mental disorder. We used partial least squares (PLS) (Krishnan et al., 2011), a multivariate technique that identifies shared associations across two high-dimensional matrices. This enables identification of dimensions of psychopathology derived from connectivity patterns in functional brain networks. Specifically, we wanted to highlight similarities and differences across dimensions derived from symptom data vs diagnostic classifications in the same sample. To do this, we investigated associations between functional connectivity and a) symptom scores, and b) diagnostic information. In addition, we investigated associations between functional connectivity and c) each diagnosis specifically, controlling for other diagnosis categories. To ensure robustness, we ran our analysis in a discovery subsample and then validated these findings in a replication sample from the same cohort. Finally, we validated the symptom dimensions of our findings in the ABCD cohort by formally comparing our results to the work by Kebets and colleagues (Kebets et al., 2023).

2. Material and methods

2.1. Sample

The sample was recruited from New York City, USA to participate in the Healthy Brain Network (HBN) (Alexander et al., 2017), a cohort consisting of children and adolescents aged 5–21. Participants were recruited through "community-referred recruitment," meaning advertisements to encourage participation of families who have concerns about in the mental health of their child. Exclusion criteria were: any present acute safety concerns (e.g., being a danger to oneself or to others), cognitive or behavioural impairments hindering participation (e.g., being nonverbal) or medical concerns that likely will confound brain-related findings.

The participants underwent a comprehensive assessment of biological and socio-environmental factors, in addition to diagnostic evaluation by qualified health personnel. After quality control and data cleaning (see below), the final sample for our analyses consisted of 1880 participants (721 females). This sample was then split into a discovery sample (80%, n = 1689) and a replication sample (20%, n = 420), matching the two subsamples on scanner location, age, sex, and diagnosis categories. See Fig. S1 for a sample flow chart. Sample demographics are provided in Fig. 1.

2.2. Clinical measures

Symptom scores were obtained from the Child Behaviour Checklist (CBCL) (Achenbach and Rescorla, 2001), which assesses emotional, behavioural, and social problems in children by parent report. Parents scored their children on 113 items as either 0 ("Not true"), 1 ("Somewhat or sometimes true") or 2 ("Very true or often true"). The responses to these items result in eight syndrome measures, previously found to be the best-fitting model for data obtained from both general and clinical populations (Achenbach and Rescorla, 2001; Ivanova et al., 2007): Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Rule-Breaking

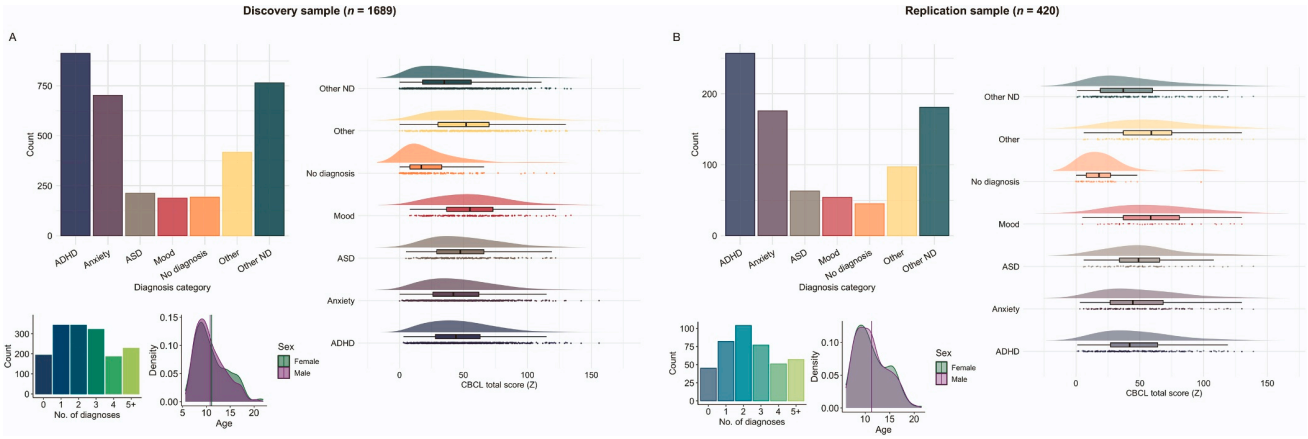

Fig. 1. Sample distributions of diagnosis categories (more than one per individual possible), total symptom burden, comorbidity, age, and sex. The lines indicate mean age for each sex. **A.** Discovery sample (n = 1689). **B.** Replication sample (n = 420). CBCL; child behaviour checklist. ADHD; attention-deficit hyperactivity disorder. ASD; autism spectrum disorder. ND; neurodevelopmental.

Behaviour, and Aggressive Behaviour.

Diagnostic information was obtained by a computerised version of the Schedule for Affective Disorders and Schizophrenia – Childrens version (KSADS) (Kaufman et al., 1997), which is a clinician-administered semi-structured psychiatric interview based on DSM-5. Based on this interview and review of all other collected materials, a consensus regarding clinical diagnosis was made by a team of licensed clinicians. We then categorised diagnoses as either "ADHD", "ASD", "anxiety disorders", "mood disorders", "other neurodevelopmental disorders", "other disorders" or "no diagnosis". Most participants had more than one diagnosis.

Of those with complete MRI data (see below), 1992 participants had available both diagnostic data and symptom data. Participants with more than 10% missing symptom data were excluded (n = 112). For the remaining participants (n = 1880), missing values were imputed with knnimpute in MATLAB (MathWorks, 2020).

2.3. MRI pre-processing

We accessed rs-fMRI and T_1-weighted structural MRI for the current study. MRI data were acquired at four different sites: a mobile scanner at Staten Island (SI), Rutgers University Brain Imaging Centre, Citigroup Biomedical Imaging Centre (CBIC) and Harlem CUNY Advanced Science Research Centre. A detailed overview of the MRI protocol is available elsewhere (http://fcon_1000.projects.nitrc.org/indi/cmi_healthy_brain_network/MRI%20Protocol.html).

T1-weighted MRI data (n = 3334) were processed using FreeSurfer v. 7.1.0 (Fischl, 2012) and quality controlled using the MRIQC classifier (Esteban et al., 2017). For participants with more than one T_1-weighted scan, we selected the sequence with the best estimated quality, as previously described (Voldsbekk et al., 2023).

For individuals with sufficient structural MRI image quality (n = 3213), we submitted rs-fMRI images for pre-processing along the following pipeline. We applied FSL MCFLIRT (Jenkinson et al., 2002) for motion correction, high-pass temporal filtering (cut-off: 100), spatial smoothing (FWHM: 6) and distortion correction as part of FEAT (Woolrich et al., 2001). The rs-fMRI images were also registered to the structural image using FLIRT (Jenkinson et al., 2002) and boundary-based registration (Greve and Fischl, 2009). Next, for additional removal of artefacts and noise, we performed non-aggressive ICA-AROMA (Pruim, Mennes, Buitelaar et al., 2015; Pruim, Mennes, van Rooij et al., 2015) and FIX (Griffanti et al., 2014; Salimi-Khorshidi et al., 2014) with a threshold of 20. During this procedure, 595 participants were excluded due to missing data or insufficient image quality. As an additional step, quality control of the raw rs-fMRI images was performed using MRIQC. Estimations of temporal signal-to-noise ratio (tSNR) and mean framewise displacement (FD), as calculated by MRIQC, were used as covariates in subsequent analyses.

2.4. Network analysis

To increase reproducibility, nodes were estimated from the Schaefer parcellation with 100 parcels and 7 networks (Schaefer et al., 2018). These networks include visual A, visual B, visual C, auditory, somatomotor A, somatomotor B, language, salience A, salience B, control A, control B, control C, default A, default B, default C, dorsal attention A and dorsal attention B. As an additional quality check of the estimated parcels, participants with data in less than 60% of voxels for each parcel were excluded (n = 290). An overview of percentage missing data in each parcel is shown in Fig. S2. To check that 60% is a reasonable threshold, balancing exclusion of participants vs completeness of voxel data, time series correlations were computed in the subset of participants with no missing data between the full parcel time series (i.e., from 100% of voxels) and parcel time series based on 60% of the voxels of that parcel (removing those voxels most frequently missing). The correlation between the full 100% parcel and the 60% parcel time series was high for every parcel (all higher than r = .87, see Fig. S3). Parcel timeseries were then imported to FSLNets (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLNets), as implemented in MATLAB (MathWorks, 2020), for estimation of edges (n = 2328). In this step, we calculated the partial correlations between nodes using L2-norm ridge regression, as these are considered a better measure of direct connectivity strength (Marrelec et al., 2006). Finally, edges were z-transformed using Fisher's transformation and we extracted the upper triangle of the correlation matrix for further analysis, yielding 4950 unique edges reflecting the connection strength between nodes for each participant.

2.5. Partial-least squares

To assess shared associations between edges (i.e., functional connectivity strength between two brain regions) and mental health data in the discovery sample, we used PLS Application (Krishnan et al., 2011), as this toolbox affords a straightforward implementation of contrasts. This approach yields latent variables (LV) reflecting maximal covariance across both matrices. See Fig. 2 for an overview of the PLS analysis pipeline. The PLS analysis estimates a cross-covariance matrix between imaging and behavioural data. This matrix is then inputted to singular value decomposition, yielding a total number of LVs corresponding to the number of behavioural variables. For each of these LVs, we get a singular value and the weights of each imaging and behavioural

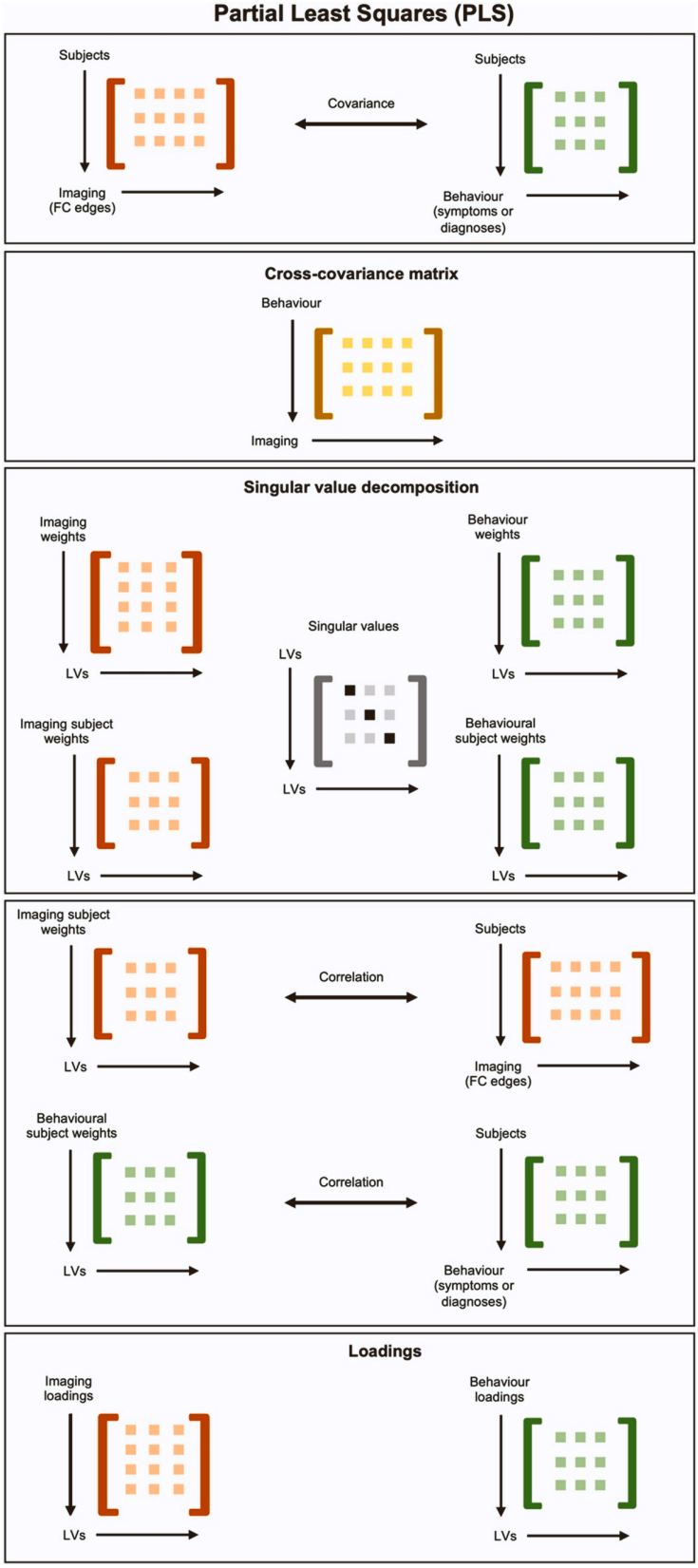

Fig. 2. Illustration of the PLS analysis pipeline. The cross-covariance matrix between imaging data and behavioural data is estimated. This matrix is then inputted to singular value decomposition, yielding singular values for each LV, as well as imaging, behavioural, and subject weights. Then, loadings onto each LV were calculated as the correlation between subject weights and the original imaging and behavioural data, respectively. PLS; partial least squares. LV; latent variable.

variable, as well as for each subject. The significance of LVs was assessed using permutation testing (n = 5000). Then, the stability of edges for each significant LV was estimated using bootstrapping with replacement (n = 1000), thresholding at |pseudo-z| > 3| (McIntosh and Lobaugh, 2004) for significance. Loadings onto each LV was then extracted as the correlation between weights on each LV and the original data. First, to investigate symptom-based patterns, we ran a rotated behavioural PLS with z-transformed symptom data as behavioural variables. Next, entering diagnostic information (one column for each diagnosis: 1 as having the diagnosis, 0 as not – more than one possible

per participant) as behavioural variables, we used the same rotated behavioural PLS approach to decompose data into putative specific and shared disorder dimensions (i.e., diagnosis-based patterns). Then, to test for diagnosis-specific patterns explicitly, we ran a non-rotated behavioural PLS, in which associations between edges and each diagnostic category was tested. This test was run for each diagnosis category separately, while controlling for all other diagnosis categories (see Table S1 for an overview of contrasts).

Prior to running PLS, edges were adjusted for sex, age, tSNR, FD, and scanner site. PLS was run using Spearmanś rank correlation. Significant LVs were then plotted using R version 4.1.2 (https://cran.r-project.org). To aid in the visualisation and interpretation of the high dimensional connectivity patterns, edges were summarised across networks for significant LVs. To investigate the loading of nodes, we also estimated the nodal loading strength across the connectivity matrix for each connectivity pattern identified by PLS using the Brain Connectivity Toolbox (Rubinov and Sporns, 2010) in MATLAB. To obtain a more detailed overview of each connectivity pattern, we plotted nodal strength and edge strength using BrainNet Viewer (Xia et al., 2013).

2.6. Consistency across age, sex, ethnicity, socio-economic status, intelligence, and medication use

Given that aberrant brain development may represent a key aetiological component in mental disorders (Casey et al., 2014; Paus et al., 2008), we assessed whether the shared associations between edges and symptom data in the discovery sample differed as a function of age or sex. To do this, we reran the symptom-based PLS without adjusting edges for age and sex. These results revealed similar patterns of covariation for all LVs except LV4, which was not found (Fig. S4). However, all LVs exhibited highly correlated feature weights across overlapping dimensions (Table S2). To examine whether the shared associations identified were generalisable across ethnic groups, we plotted the correlations between edges and symptoms by ethnic group (Fig. S5). Similarly, to examine whether the shared associations identified were generalisable across levels of socioeconomic status (SES), we plotted the correlations by median-split of household income, as a proxy for SES (Fig. S6). To examine whether the shared associations identified were generalisable across levels of intelligence, we plotted the correlations by full scale IQ split into ± 70 (Fig. S7). To examine whether the shared associations identified were generalisable across current use of psychiatric medication or not, we plotted the correlations by current use vs no use (yes/no; 310 participants reported yes) (Fig. S8). Finally, symptom weights and connectivity weights from the symptom-based PLS were regressed against each diagnosis category separately, with “no diagnosis” as a reference group. We also regressed weights against number of diagnoses, interpreting the latter as a proxy of cross-diagnostic vulnerability. All associations were adjusted for age, age^2, and sex.

2.7. Validation in replication sample

To test whether the results were robust and reliable, we repeated the PLS analysis in the replication sample. Akin to previous work (Linke et al., 2021), weights estimated in each subsample were then multiplied with input data from the other subsample to derive subject weights for participants whose data was not part of the model estimations. Replication was determined as the Pearson’s correlation of the derived subject weights for each dataset with those estimated in the corresponding subset. To establish significance of the correlations, we ran permutations (n = 5000) and results were considered replicable if correlations in both directions were significant.

2.8. Validation in independent cohort

To test whether the results also generalise to other cohorts, we formally tested the replicability of previous work in the ABCD cohort (Kebets et al., 2023) to the current sample. Specifically, we repeated the replication procedure described above, this time applying weights from the ABCD dataset to input data from HBN and correlated this product with subject weights from our symptom-based PLS analysis. Of note, as the previous work utilised the Schaefer parcellation with 400 parcels and submitted these to PCA prior to running PLS, we first decomposed the HBN data by multiplying 400 parcellated HBN data with PCA weights estimated in the ABCD analysis.

3. Results

3.1. Symptom-based dimensions

Based on the scree plot of percent cross-block covariance explained (Fig. S9), we selected the first six LVs in the symptom-based PLS in the discovery sample for further analysis. Of these, five were significant (r = 0.72, p = .045; r = 0.65, p = .026; r = 0.75, p = .009; r = 0.71, p = .031; r = 0.62, p = .003, respectively; Fig. S10). Each LV represents a distinct pattern that relates a weighted set of symptoms to a weighted set of functional brain network connections. Inspection of the most heavily weighted symptoms for each LV revealed that they resemble the psychopathology hierarchy: the first LV resembled a general psychopathology factor (see Fig. 3 A), while the remaining four represented increasingly narrow dimensions (see Fig. 4).

Specifically, LV2 was related to internalising- externalising, LV3 to neurodevelopment, LV4 to somatic complaints, and LV6 to thought problems.

These psychopathology dimensions were identified by their shared associations with specific patterns of connectivity. For each dimension, these patterns were widely distributed across functional networks (see Fig. 3 and S11). LV1 was related to weaker connectivity between the salience and limbic network, and between the limbic network and DMN, as well as within the control network (Fig. 3B-C). In addition, LV1 was related to stronger connectivity between the limbic and visual network and between the salience network and DMN. The nodes with strongest loading on this pattern implicated the control network, DMN, and salience network. LV2 was related to stronger within- and between-network connectivity in the visual network and lower connectivity within and between the salience network and DMN. The strongest nodes in LV2 were in the DMN, control and DA network (Fig. S11). LV3 was related to stronger connectivity between the somatomotor and visual network and to lower connectivity between the limbic network and control network. The strongest nodes were distributed across the DMN, control, and visual network. LV4 was related to weaker connectivity between the DA and control network, stronger connectivity between the visual and limbic network, and within the DA and somatomotor network. The strongest nodes were in the DA network. LV6 was related to weaker connectivity between the limbic and visual network and between the visual network and the DA network, as well as between the somatomotor network and DMN. The strongest nodes were in the control network and DA network.

3.2. Diagnosis-based dimensions

The rotated diagnosis-based PLS identified one significant LV

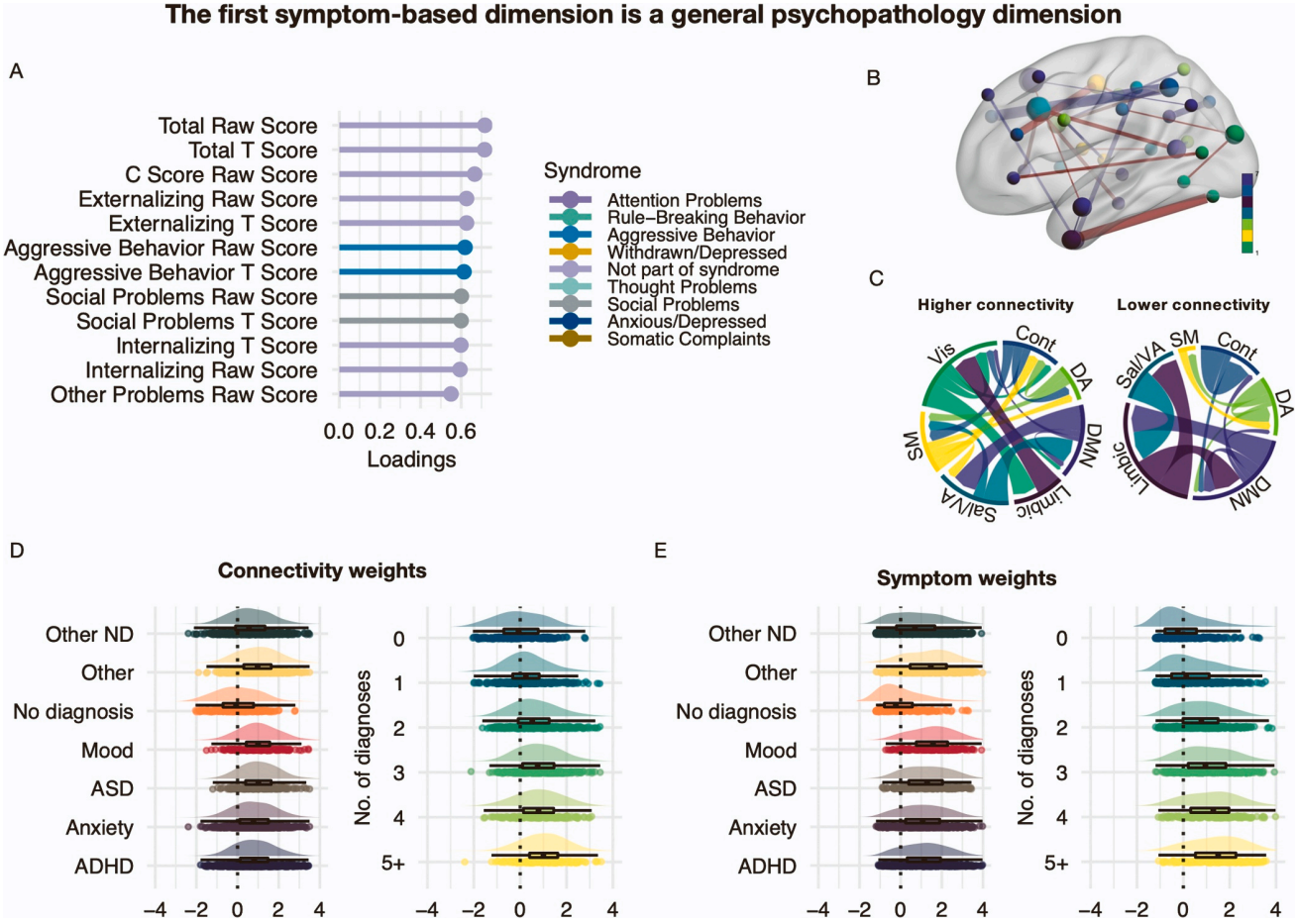

Fig. 3. The first dimension of shared associations between functional connectivity and clinical symptoms resembled a general psychopathology factor. **A.** The highest loading symptoms of this dimension. Loadings reflect correlations between LV weights and original data. **B.** Strength of edges and nodes that contributed to this dimension. Edges are coloured red for higher connectivity and blue for lower connectivity. Nodes are coloured based on network membership. **C.** Both increased and reduced connectivity in specific edges contributed. Magnitude in this plot reflects summarised edge strength across each network. D-**E.** Connectivity and symptom weights across diagnostic categories (left) and number of comorbidities (right). In these plots, the data is centred around the mean of no diagnosis. LV; latent variable. ADHD; attention-deficit hyperactivity disorder. ASD; autism spectrum disorder. ND; neurodevelopmental. Vis; visual network. SM; somatomotor network. Sal/VA; salience network. Cont; control network. DMN; default mode network. DA; dorsal attention network.

($r = 0.68$, $p = .009$). As shown in Fig. 5 A, this pattern resembled a general case vs control pattern across all diagnoses. Partly consistent with the general psychopathology pattern of the symptom-based LV1, a higher loading on this LV (i.e., having a diagnosis) entailed stronger connectivity between the limbic and visual and salience network, in addition to weaker connectivity between the salience network and DMN (Fig. 5B-C). The strongest nodes were distributed across all these networks.

3.3. Diagnosis-specific patterns

The non-rotated diagnosis-specific PLS, which tested each diagnosis category separately while controlling for all other diagnosis categories, identified a unique connectivity pattern for ASD ($r = 0.44$, $p = .012$). As shown in Fig. 6, the ASD-specific pattern was widely distributed, including weaker connectivity within the somatomotor network and between the DA network and visual network. The strongest nodes implicated the salience, visual, and

DA network. In addition, the non-rotated diagnosis-specific PLS identified a unique pattern of no diagnosis vs all diagnoses ($r = 0.56$, $p = .012$) (Fig. S12). This pattern implicated increased connectivity between the somatomotor, and salience and DA network, in addition to lower connectivity between the visual and limbic network. The strongest nodes implicated in this pattern were in the salience and somatoform network. The remaining diagnosis categories did not show disorder-specific patterns of functional connectivity.

3.4. Symptom-based pattern evident across diagnostic boundaries

To understand the distribution of symptom dimensions in more detail, we plotted them against diagnosis categories (Fig. S13). As shown in Fig. 3E-F, there was a consistency between a higher degree of co-morbidity and higher weights on LV1. We also observed expected variation in symptom weights with respect to specific diagnoses, such as patients with ADHD and ASD loading more highly on the neuro-developmental dimension (LV3; Fig. S13). On the internalising-externalising dimension (LV2), mood disorder, ASD, and anxiety disorder loaded more negatively, consistent with increasing symptoms of internalising being typical for these diagnosis categories. In addition, linear models revealed that all diagnosis categories showed higher symptom and connectivity weights on LV1 compared to having no diagnosis (Table S3). There was also a significant linear association with the number of diagnoses for both symptom and connectivity weights on LV1 (Table S4 and S5). This was true when including "no diagnosis" in the model or not, suggesting that this effect was not driven by case-control effects.

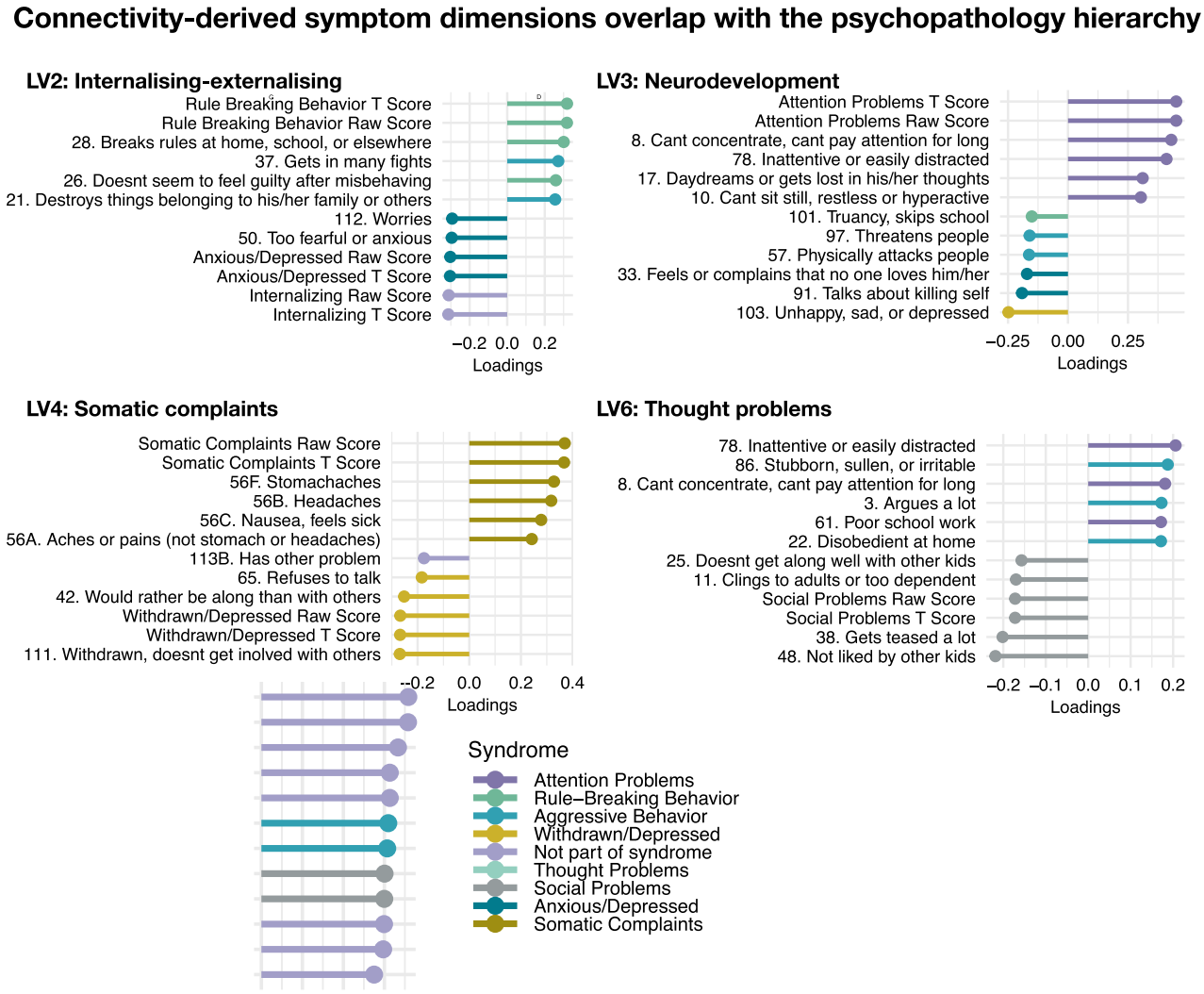

Fig. 4. Dimensions of shared associations between functional connectivity and clinical symptoms map onto the hierarchical structure of psychopathology. **A.** LV2 map onto symptoms of higher externalisation and lower internalisation. **B.** LV3 map onto symptoms of neurodevelopmental problems. **C.** LV4 map onto symptoms of higher somatic complaints and lower withdrawn/depressive symptoms. **D.** LV6 map onto symptoms of higher thought problems. Colours reflect CBCL syndrome measures. LV; latent variable. CBCL; Child behaviour checklist.

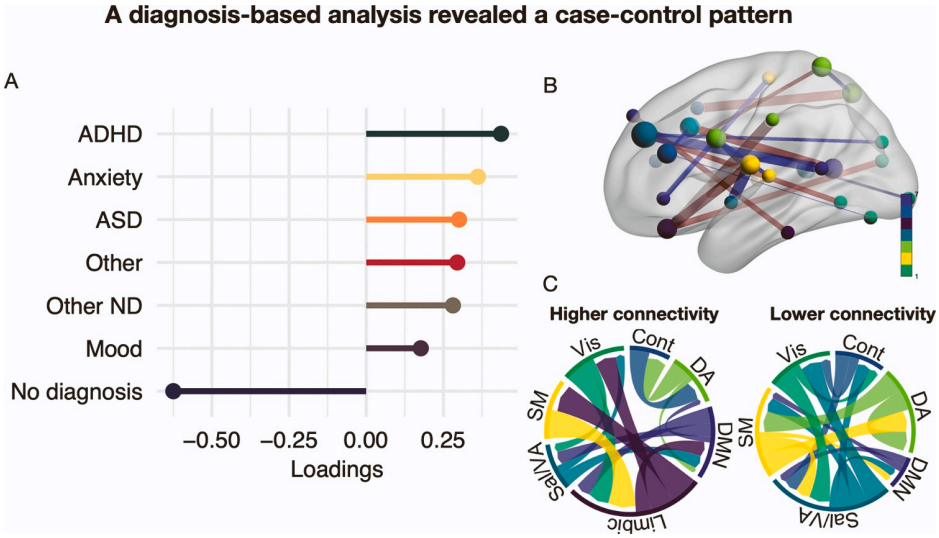

Fig. 5. One dimension of shared associations between functional connectivity and diagnosis categories, resembling a cross-diagnostic case-control difference. **A.** The diagnosis dimension reflected a pattern across all diagnostic categories vs no diagnosis. **B.** Strength of edges and nodes that contributed to this dimension. Edges are coloured red for higher connectivity and blue for lower connectivity. Nodes are coloured based on network membership. **C.** Both increased and reduced connectivity in specific edges contributed. Magnitude in this plot reflects summarised edge strength across each network. ADHD; attention-deficit hyperactivity disorder. ND; neurodevelopmental. ASD; autism spectrum disorder. Vis; visual network. SM; somatomotor network. Sal/VA; salience network. Cont; control network. DMN; default mode network. DA; dorsal attention network.

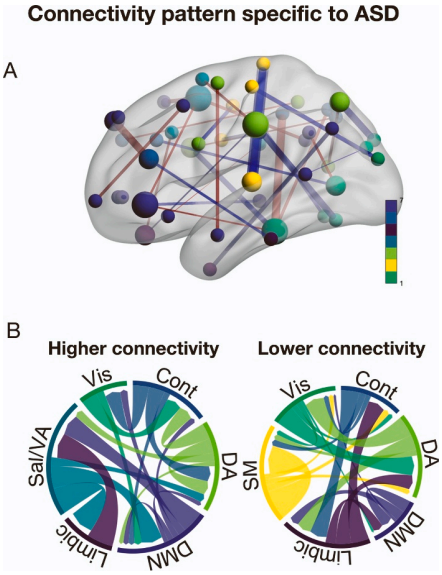

Fig. 6. ASD was the only diagnosis category exhibiting a unique pattern of connectivity **A.** Strength of edges and nodes specific to ASD. Edges are coloured red for higher connectivity and blue for lower connectivity. Nodes are coloured based on network membership. **B.** Both increased and reduced connectivity in specific edges contributed. Magnitude in this plot reflects summarised edge strength across each network. ASD; autism spectrum disorder. Vis; visual network. SM; somatomotor network. Sal/VA; salience network. Cont; control network. DMN; default mode network. DA; dorsal attention network.

3.5. Validation in replication sample

The symptom item weights from the symptom-based PLS were validated in the replication sample (Fig. S14). For LV1-LV3, the correlations between replication and discovery and vice versa were high ($r = 0.91–0.99$, all $p = .001$), while the correlations for LV4 and LV6 were lower ($r = 0.13–0.20$, all $p = .001$, and $r = 0.10–0.15$, $p < .016$, respectively). The connectivity weights for LV2, LV3 and LV6 were also significantly correlated ($r = 0.08–0.18$, $p < .025$), while LV1 and LV4 did not replicate ($r = 0.04–0.14$, $p = .001–0.18$) (Fig. S14). Of note, the association between connectivity weights for LV1 and LV4 were correlated between replication-derived discovery weights and original discovery weights, while the opposite direction was not.

For the diagnosis-based PLS and the diagnosis-specific PLS, a similar pattern emerged. The diagnosis weights in the diagnosis-based PLS were replicated across the discovery and replication samples (both $r = 0.99$, $p = .001$), while the connectivity weights were not ($r > 0.06$, $p = .002–0.094$) (Fig. S15). For the ASD-specific pattern derived in the diagnosis-specific PLS, the connectivity weights were validated across samples ($r = 0.20–0.21$, both $p = .001$), while no diagnosis-specific connectivity weights were not replicated (both $r = 0.04$, $p = .07–0.20$) (Fig. S16).

3.6. Validation in independent cohort

The application of ABCD-derived PLS weights to HBN data revealed replication of all five symptom LVs in the symptom-based PLS across cohorts. As shown in Fig. 7, the LV1-LV3 symptom weights were highly correlated ($r = 0.86–0.98$, all $p = .001$), while LV4 and LV6 exhibited lower correlations ($r = 0.12$, $p = .001$, and $r = 0.21$, $p = .001$, respectively). The connectivity weights did not replicate ($r = 0.001–0.02$, $p > .18$).

4. Discussion

Through shared associations between mental health data and functional connectivity, the current study delineated shared and unique patterns in child and adolescent functional brain networks. We found that dimensions of clinical symptoms map onto specific patterns of brain connectivity, aligned with the psychopathology hierarchy. The rotated decomposition of diagnostic data (i.e., the diagnosis-based PLS) revealed one significant dimension, implicating a cross-diagnostic pattern. The disorder-specific tests revealed specific patterns of connectivity related to ASD and no diagnosis (i.e., a case-control disorder-general effect), but not for any other diagnosis. For the symptom-based dimensions, we found that higher comorbidity was consistently related to both increased symptom burden and increased connectivity aberrations. Critically, these clinical patterns were replicable in an independent sample from the same cohort, as well as in an independent cohort, supporting the robustness and generalisability of our findings. Consistent with previous work (Linke et al., 2021), the connectivity patterns were not replicable to the same extent. Taken together, these results indicate that compared to diagnostic classifications in isolation, transdiagnostic and symptom-based dimensions of psychopathology are more closely mapped to the functional networks of the brain during the formative years of childhood and adolescence.

The clinical dimensions revealed by shared associations between functional connectivity and symptoms in the current study adhere to the hierarchical structure of psychopathology, implicating a general psychopathology factor, followed by dimensions of internalising- externalising, neurodevelopment, somatic complaints, and thought problems. PLS derives orthogonal LVs, leaving dimensions independent. Capturing internalisation- externalisation as the second latent pattern is consistent with previous work (Kebets et al., 2023; Linke et al., 2021). Indeed, we did not only detect overlapping symptom-based dimensions as those previously identified by Kebets and colleagues (Kebets et al., 2023), we were able to replicate them in our sample. This replication across samples is striking, suggesting generalisable patterns of functional connectivity-psychopathology associations, and strongly supporting the conceptualisation of the general population vs clinical populations as existing on a continuum. Interestingly, given the overlap between the current functional connectivity-derived symptom dimensions and CBCL subscale syndromes derived from symptom data alone, it appears that the psychopathology hierarchy is represented in functional networks during development.

In contrast to our findings, Linke and colleagues (Linke et al., 2021) identified a dimension specific to anxiety symptoms. Neither did we detect a pattern specific to having an anxiety diagnosis. This discrepancy may reflect diversity in the range of symptoms and diagnostic groups included. Indeed, in the current study, the diagnostic range was broader than in the study by Linke and colleagues (Linke et al., 2021). Concurrently, the symptom domains assessed by Xia and colleagues (Xia et al., 2018) were more closely mapped to adult psychopathology than to child symptomology, which may explain the differences in clinical dimensions derived. Although the age range is largely overlapping between the current sample and the sample used by Xia and colleagues, the current sample had a mean age of 10.5 years, while the previous study had a mean age of 15.82 years. Consistent with this difference in age, the diagnoses and symptoms prevalent in the current sample were neurodevelopmental and early emerging psychopathologies, such as attention problems, autism, and anxiety, while the sample used by Xia et al. (2018) present symptomatology more closely resembling distributions seen in adolescent and adult samples, including all those childhood categories, but also markedly higher prevalence of symptoms of mood disorders and emerging psychosis (Alnaes et al., 2018). It is not unreasonable to expect this difference in symptom distribution to yield differences in the clinical dimensions derived in the current work compared to the previous study. In addition, the current study included CBCL summary scores, alongside item scores. This may have influenced

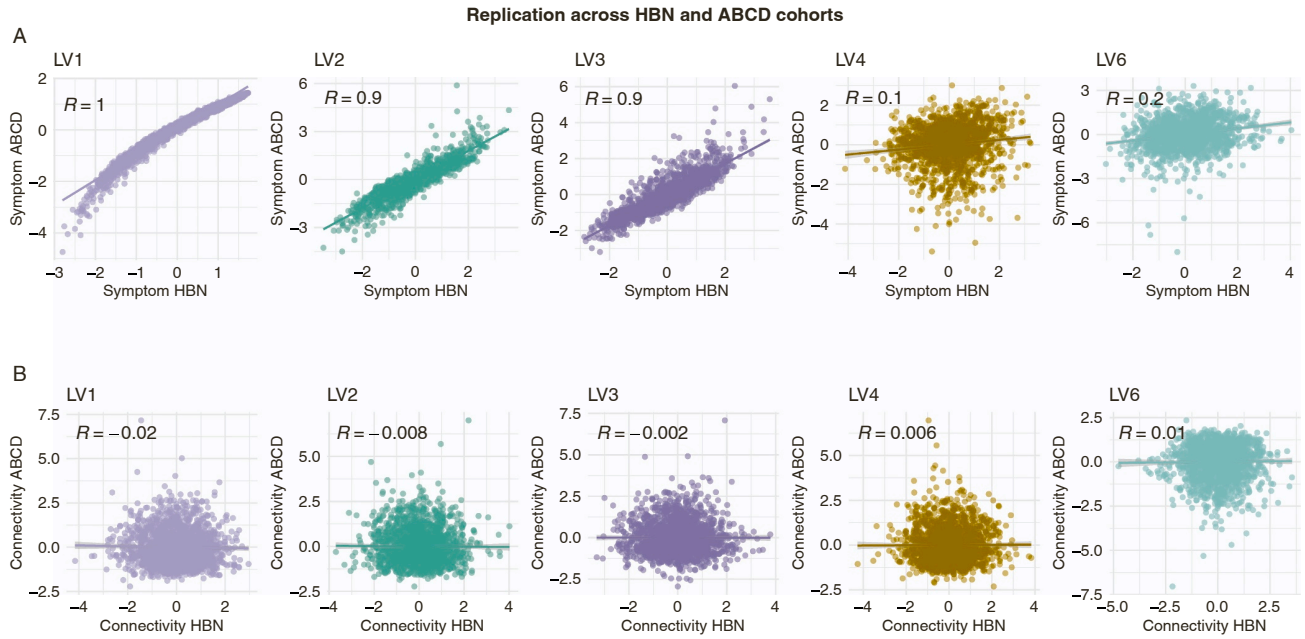

Fig. 7. Correlations between PLS weights derived in the ABCD cohort and in the current sample (i.e., HBN). **A.** Symptom weights were significantly associated across ABCD and HBN cohorts. **B.** Connectivity weights were not significantly associated. PLS; partial least squares. ABCD; adolescent brain cognitive development cohort. HBN; healthy brain network cohort.

the way our model structured the associations, which may also explain why we obtain different results.

Alterations in functional connectivity of the DMN have previously been implicated in several neurological and mental disorders (van den Heuvel and Sporns, 2019). In addition, DMN connectivity has been linked to general psychopathology (Elliott et al., 2018; Karcher et al., 2021; Kebets et al., 2023; Sato et al., 2018). In line with this, DMN nodes were some of the strongest loading nodes and edges of the general psychopathology factor (i.e. symptom-based LV1) in the current study. This factor was further characterised by a distributed pattern involving weaker connectivity between the limbic network and salience network and DMN. It also implicated stronger connectivity between DMN and salience network, and between the control network and somatomotor network. In line with this, the limbic, salience, fronto-parietal and sensorimotor networks are also implicated in general psychopathology (Vanes and Dolan, 2021).

The connectivity pattern related to a general psychopathology factor in the ABCD sample (Kebets et al., 2023) implicated increased connectivity between the DMN and salience network, which was also a key finding in the current sample. However, this pattern was not replicable across cohorts when formally comparing them. The lack of generalisability of connectivity patterns across cohorts is consistent with previous replication attempts across cohorts (Linke et al., 2021). This study showed that while connectivity-informed clinical dimensions were replicable across two cohorts, the connectivity patterns themselves were less so (Linke et al., 2021). The authors attributed this to a "many--to-one" mapping between neural and clinical variables, which may also explain the lack of overlap in specific connectivity patterns identified in the current work compared to previous work.

The diagnosis-based analysis revealed only one significant dimension, resembling a cross-diagnostic case-control pattern. This pattern was characterised by no diagnosis exhibiting the highest loading, with all the other diagnosis categories exhibiting smaller associations in the opposite direction. If, instead, connectivity patterns specific to each diagnosis were detectable, we would have expected this test to reveal several dimensions (i.e., LVs), each consisting of loadings from one (or a few) diagnoses. In addition, we identified a no diagnosis vs all diagnoses specific pattern, representing an inverse cross-diagnostic case-control pattern. Although the weighting of each diagnosis category differed between these two analyses, the overarching connectivity patterns for these dimensions revealed inverse overlap. Indeed, although the symptom-based general psychopathology dimension exhibited a more distributed connectivity pattern, there was also some overlap between this pattern and cross-diagnostic case-control pattern. Together, these patterns implicate a distributed connectivity pattern implicating several key networks, such as the salience network and the limbic network, in separating no diagnosis from having a diagnosis.

ASD was the only diagnosis category exhibiting a detectable unique pattern of connectivity. This pattern was widely distributed, implicating altered connectivity within several brain networks. Hyperconnectivity within several large-scale brain networks has previously been implicated in ASD (Uddin et al., 2019). The distributed nature of the ASD-specific pattern identified in the current study, including both increased and reduced connectivity within and between several networks, is in line with the notion that both hyperconnectivity and hypoconnectivity may underlie ASD (Kana et al., 2011). Importantly, the finding that ASD was the only diagnosis group exhibiting a unique connectivity pattern has implications for our understanding of the neurobiological substrates of ASD, but also for our understanding of the structure of psychopathology and ASD in this landscape more broadly. The current work supports the understanding that rather than belonging in the general psychopathology domain, ASD likely represent a separate neurodevelopmental dimension (Opel et al., 2020b; Ronald, 2019).

Although our findings provide several new insights into the link between functional brain connectivity and the structure of childhood psychopathology, some limitations should be noted. First, functional connectivity results are known to be influenced by methodological choices (Li et al., 2021; Sala-Llonch et al., 2019; Shirer et al., 2015), complicating the identification of robust and replicable results. To increase replicability of the current work, we relied on an established parcellation scheme (Schaefer et al., 2018). Critically, we also validated our findings in both an independent sample from the same cohort, as well as in an independent cohort. Second, several functional connectivity patterns identified implicated the limbic network, a network

known to be sensitive to susceptibility artefacts and reduced signal (Khatamian et al., 2016). Although we did additional measures to reduce the influence of reduced signal on our analysis, we cannot completely rule out that our results are influenced by this confound. Third, as the sample consisted of mainly children, and most of them with at least one mental disorder, motion was an issue. To ameliorate this influence, we used the MRIQC classifier to exclude participants with insufficient image quality, cleaned data using FIX and AROMA, and regressed out measures of image quality and motion from the data. Fourth, the cross-sectional nature of the study design prohibits any conclusion to be drawn with respect to the within-person temporal dynamics of any identified pattern. Fifth, given that the symptom data was continuous, and the diagnostic analysis separated the sample into dichotomous groups, the power to extract maximal covariance between symptoms and functional connectivity was better than that for the diagnostic analysis. As such, these results cannot be directly compared. Finally, the sample was enriched with children diagnosed with ADHD and other neurodevelopmental conditions. Although this may be representative of a developmental clinical sample, it may not generalise to other clinical populations. For example, this has implications for the comparison of the current results to other studies investigating a derived general psychopathology factor. However, given that we could replicate previous work in a population-based sample in the current sample, our findings seem to generalise to other populations, which is a strength of the current study.

5. Conclusions

The current work found that dimensions of psychopathology derived from clinical symptoms were associated with specific patterns of functional connectivity in the developing brain, while ASD was the only diagnostic category to exhibit such a specific pattern. This contributes to a growing body of evidence in favour of dimensional and transdiagnostic classifications of psychopathology (Vanes and Dolan, 2021). In this classification, neurodevelopmental conditions such as ASD may possess specific abnormalities in functional connectivity networks above and beyond those related to general psychopathology. This has implications for the pursuit of individualised brain-based surrogate markers in mental health research and care, which in turn may lead to improved prevention and intervention of mental disorders.

Declaration of Competing Interest

O.A.A. is a consultant to cortechs.ai and has received speaker's honorarium from Janssen, Lundbeck, Sunovion.

Data Availability

The data that forms the basis of this work were obtained from the open access Healthy Brain Network (http://fcon_1000.projects.nitrc.org/indi/cmi_healthy_brain_network/). The code used in the study is available at: https://osf.io/gt9dk/.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dcn.2023.101271.

References

Achenbach, T.M., Rescorla, L.A., 2001. Manual for the ASEBA school-age forms & profiles: an integrated system of multi-informant assessment Burlington. Research Center for Children, Youth, & Families. University of Vermont, VT, p. *1617*.

Alexander, L.M., Escalera, J., Ai, L., Andreotti, C., Febre, K., Mangone, A., Vega-Potler, N., Langer, N., Alexander, A., Kovacs, M., 2017. An open resource for transdiagnostic research in pediatric mental health and learning disorders. Sci. Data 4 (1), 1–26.

Alnaes, D., Kaufmann, T., Doan, N.T., Cordova-Palomera, A., Wang, Y., Bettella, F., Moberget, T., Andreassen, O.A., Westlye, L.T., 2018. Association of heritable cognitive ability and psychopathology with white matter properties in children and adolescents. JAMA Psychiatry 75 (3), 287–295. https://doi.org/10.1001/jamapsychiatry.2017.4277.

Casey, B.J., Oliveri, M.E., Insel, T., 2014. A neurodevelopmental perspective on the research domain criteria (RDoC) framework. Biol. Psychiatry 76 (5), 350–353. https://doi.org/10.1016/j.biopsych.2014.01.006.

Casey, B.J., Cannonier, T., Conley, M.I., Cohen, A.O., Barch, D.M., Heitzeg, M.M., Soules, M.E., Teslovich, T., Dellarco, D.V., Garavan, H., 2018. The adolescent brain cognitive development (ABCD) study: imaging acquisition across 21 sites. Dev. Cogn. Neurosci. 32, 43–54.

Caspi, A., Houts, R.M., Belsky, D.W., Goldman-Mellor, S.J., Harrington, H., Israel, S., Meier, M.H., Ramrakha, S., Shalev, I., Poulton, R., Moffitt, T.E., 2014. The p factor: one general psychopathology factor in the structure of psychiatric disorders? Clin. Psychol. Sci. 2 (2), 119–137. https://doi.org/10.1177/2167702613497473.

Caspi, A., Houts, R.M., Ambler, A., Danese, A., Elliott, M.L., Hariri, A., Harrington, H., Hogan, S., Poulton, R., Ramrakha, S., Rasmussen, L.J.H., Reuben, A., Richmond-Rakerd, L., Sugden, K., Wertz, J., Williams, B.S., Moffitt, T.E., 2020. Longitudinal assessment of mental health disorders and comorbidities across 4 decades among participants in the dunedin birth cohort study. e203221-e203221 JAMA Netw. Open 3 (4). https://doi.org/10.1001/jamanetworkopen.2020.3221.

Elliott, M.L., Romer, A., Knodt, A.R., Hariri, A.R., 2018. A connectome-wide functional signature of transdiagnostic risk for mental illness. Biol. Psychiatry 84 (6), 452–459. https://doi.org/10.1016/j.biopsych.2018.03.012.

Esteban, O., Birman, D., Schaer, M., Koyejo, O.O., Poldrack, R.A., Gorgolewski, K.J., 2017. MRIQC: advancing the automatic prediction of image quality in MRI from unseen sites. PLoS One 12 (9), e0184661. https://doi.org/10.1371/journal.pone.0184661.

Fischl, B., 2012. FreeSurfer. NeuroImage 62 (2), 774–781. https://doi.org/10.1016/j.neuroimage.2012.01.021.

Goodkind, M., Eickhoff, S.B., Oathes, D.J., Jiang, Y., Chang, A., Jones-Hagata, L.B., Ortega, B.N., Zaiko, Y.V., Roach, E.L., Korgaonkar, M.S., Grieve, S.M., Galatzer-Levy, I., Fox, P.T., Etkin, A., 2015. Identification of a Common Neurobiological Substrate for Mental Illness. JAMA Psychiatry 72 (4), 305–315. https://doi.org/10.1001/jamapsychiatry.2014.2206.

Greve, D.N., Fischl, B., 2009. Accurate and robust brain image alignment using boundary-based registration. NeuroImage 48 (1), 63–72. https://doi.org/10.1016/j.neuroimage.2009.06.060.

Griffanti, L., Salimi-Khorshidi, G., Beckmann, C.F., Auerbach, E.J., Douaud, G., Sexton, C. E., Zsoldos, E., Ebmeier, K.P., Filippini, N., Mackay, C.E., Moeller, S., Xu, J., Yacoub, E., Baselli, G., Ugurbil, K., Miller, K.L., Smith, S.M., 2014. ICA-based artefact removal and accelerated fMRI acquisition for improved resting state network imaging. NeuroImage 95, 232–247. https://doi.org/10.1016/j.neuroimage.2014.03.034.

van den Heuvel, M.P., Sporns, O., 2019. A cross-disorder connectome landscape of brain dysconnectivity. Nat. Rev. Neurosci. 20 (7), 435–446. https://doi.org/10.1038/s41583-019-0177-6.

Hindley, G., Frei, O., Shadrin, A.A., Cheng, W., O'Connell, K.S., Icick, R., Parker, N., Bahrami, S., Karadag, N., Roelfs, D., Holen, B., Lin, A., Fan, C.C., Djurovic, S., Dale, A.M., Smeland, O.B., Andreassen, O.A., 2022. Charting the landscape of genetic overlap between mental disorders and related traits beyond genetic correlation. Am. J. Psychiatry 179 (11), 833–843. https://doi.org/10.1176/appi.ajp.21101051.

Insel, T.R., Cuthbert, B.N., 2015. Brain disorders? precisely. Science 348 (6234), 499–500.

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D.S., Quinn, K., Wang, P., 2010. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. American Journal of psychiatry 167 (7), 748–751.

Ivanova, M.Y., Achenbach, T.M., Dumenci, L., Rescorla, L.A., Almqvist, F., Weintraub, S., Bilenberg, N., Bird, H., Chen, W.J., Dobrean, A., Döpfner, M., Erol, N., Fombonne, E.,

Fonseca, A.C., Frigerio, A., Grietens, H., Hannesdóttir, H., Kanbayashi, Y., Lambert, M., Larsson, B., Leung, P., Liu, X., Minaei, A., Mulatu, M.S., Novik, T.S., Oh, K.J., Roussos, A., Sawyer, M., Simsek, Z., Steinhausen, H.-C., Metzke, C.W., Wolanczyk, T., Yang, H.-J., Zilber, N., Zukauskiene, R., Verhulst, F.C., 2007. Testing the 8-syndrome structure of the child behavior checklist in 30 societies. J. Clin. Child Adolesc. Psychol. 36 (3), 405–417. https://doi.org/10.1080/15374410701444363.

Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. NeuroImage 17 (2), 825–841. https://doi.org/10.1016/S1053-8119(02)91132-8.

Kana, R.K., Libero, L.E., Moore, M.S., 2011. Disrupted cortical connectivity theory as an explanatory model for autism spectrum disorders. Phys. Life Rev. 8 (4), 410–437. https://doi.org/10.1016/j.plrev.2011.10.001.

Karcher, N.R., Michelini, G., Kotov, R., Barch, D.M., 2021. Associations between resting-state functional connectivity and a hierarchical dimensional structure of psychopathology in middle childhood. Biol. Psychiatry.: Cogn. Neurosci. Neuroimaging 6 (5), 508–517. https://doi.org/10.1016/j.bpsc.2020.09.008.

Kaufman, J., Birmaher, B., Brent, D., Rao, U.M.A., Flynn, C., Moreci, P., Williamson, D., Ryan, N., 1997. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. J. Am. Acad. Child Adolesc. Psychiatry 36 (7), 980–988. https://doi.org/10.1097/00004583-199707000-00021.

Kebets, V., Piguet, C., Chen, J., Ooi, L.Q.R., Kirschner, M., Siffredi, V., Misic, B., Yeo, B. T., Bernhardt, B., 2023. Multimodal neural correlates of childhood psychopathology. *bioRxiv* 2002, 530821.

Kessler, R.C., Angermeyer, M., Anthony, J.C., De Graaf, R., Demyttenaere, K., Gasquet, I., De Girolamo, G., Gluzman, S., Gureje, O., Haro, J.M., 2007. Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. World Psychiatry 6 (3), 168.

Khatamian, Y.B., Golestani, A.M., Ragot, D.M., Chen, J.J., 2016. Spin-echo resting-state functional connectivity in high-susceptibility regions: accuracy, reliability, and the impact of physiological noise. Brain Connect. 6 (4), 283–297. https://doi.org/10.1089/brain.2015.0365.

Kotov, R., Krueger, R.F., Watson, D., Achenbach, T.M., Althoff, R.R., Bagby, R.M., Brown, T.A., Carpenter, W.T., Caspi, A., Clark, L.A., 2017. The hierarchical taxonomy of psychopathology (HiTOP): a dimensional alternative to traditional nosologies. J. Abnorm. Psychol. 126 (4), 454.

Krishnan, A., Williams, L.J., McIntosh, A.R., Abdi, H., 2011. Partial Least Squares (PLS) methods for neuroimaging: A tutorial and review. NeuroImage 56 (2), 455–475. https://doi.org/10.1016/j.neuroimage.2010.07.034.

Lahey, B.B., Van Hulle, C.A., Singh, A.L., Waldman, I.D., Rathouz, P.J., 2011. Higher-order genetic and environmental structure of prevalent forms of child and adolescent psychopathology. Arch. Gen. Psychiatry 68 (2), 181–189. https://doi.org/10.1001/archgenpsychiatry.2010.192.

Lahey, B.B., Krueger, R.F., Rathouz, P.J., Waldman, I.D., Zald, D.H., 2017. A hierarchical causal taxonomy of psychopathology across the life span. Psychol. Bull. 143 (2), 142–186. https://doi.org/10.1037/bul0000069.

Lees, B., Squeglia, L.M., McTeague, L.M., Forbes, M.K., Krueger, R.F., Sunderland, M., Baillie, A.J., Koch, F., Teesson, M., Mewton, L., 2021. Altered neurocognitive functional connectivity and activation patterns underlie psychopathology in preadolescence. Biol. Psychiatry.: Cogn. Neurosci. Neuroimaging 6 (4), 387–398. https://doi.org/10.1016/j.bpsc.2020.09.007.

Li, X., Ai, L., Giavasis, S., Jin, H., Feczko, E., Xu, T., Clucas, J., Franco, A., Sólon Heinsfeld, A., Adebimpe, A., 2021. Moving beyond processing and analysis-related variation in neuroscience. *bioRxiv* 2001, 470790.

Linke, J.O., Abend, R., Kircanski, K., Clayton, M., Stavish, C., Benson, B.E., Brotman, M. A., Renaud, O., Smith, S.M., Nichols, T.E., Leibenluft, E., Winkler, A.M., Pine, D.S., 2021. Shared and anxiety-specific pediatric psychopathology dimensions manifest distributed neural correlates. Biol. Psychiatry 89 (6), 579–587. https://doi.org/10.1016/j.biopsych.2020.10.018.

Marrelec, G., Krainik, A., Duffau, H., Pélégrini-Issac, M., Lehéricy, S., Doyon, J., Benali, H., 2006. Partial correlation for functional brain interactivity investigation in functional MRI. NeuroImage 32 (1), 228–237.

MathWorks. (2020). *MATLAB*. In.

McIntosh, A.R., Lobaugh, N.J., 2004. Partial least squares analysis of neuroimaging data: applications and advances. NeuroImage 23, S250–S263.

McTeague, L.M., Huemer, J., Carreon, D.M., Jiang, Y., Eickhoff, S.B., Etkin, A., 2017. Identification of common neural circuit disruptions in cognitive control across psychiatric disorders. Am. J. Psychiatry 174 (7), 676–685. https://doi.org/10.1176/appi.ajp.2017.16040400.

McTeague, L.M., Rosenberg, B.M., Lopez, J.W., Carreon, D.M., Huemer, J., Jiang, Y., Chick, C.F., Eickhoff, S.B., Etkin, A., 2020. Identification of common neural circuit disruptions in emotional processing across psychiatric disorders. Am. J. Psychiatry 177 (5), 411–421.

Michelini, G., Barch, D.M., Tian, Y., Watson, D., Klein, D.N., Kotov, R., 2019. Delineating and validating higher-order dimensions of psychopathology in the adolescent brain cognitive development (ABCD) study. Transl. Psychiatry 9 (1), 261. https://doi.org/10.1038/s41398-019-0593-4.

Opel, N., Goltermann, J., Hermesdorf, M., Berger, K., Baune, B.T., Dannlowski, U., 2020a. Cross-disorder analysis of brain structural abnormalities in six major psychiatric disorders: A secondary analysis of mega- and meta-analytical findings from the ENIGMA consortium. Biol. Psychiatry 88 (9), 678–686. https://doi.org/10.1016/j.biopsych.2020.04.027.

Opel, N., Goltermann, J., Hermesdorf, M., Berger, K., Baune, B.T., Dannlowski, U., 2020b. Cross-disorder analysis of brain structural abnormalities in six major psychiatric disorders: a secondary analysis of mega-and meta-analytical findings from the ENIGMA consortium. Biol. Psychiatry 88 (9), 678–686.

Paus, T., Keshavan, M., Giedd, J.N., 2008. Why do many psychiatric disorders emerge during adolescence. Nat. Rev. Neurosci. 9 (12), 947–957. https://doi.org/10.1038/nrn2513.

Pettersson, E., Larsson, H., Lichtenstein, P., 2016. Common psychiatric disorders share the same genetic origin: a multivariate sibling study of the Swedish population. Mol. Psychiatry 21 (5), 717–721. https://doi.org/10.1038/mp.2015.116.

Power, J.D., Fair, D.A., Schlaggar, B.L., Petersen, S.E., 2010. The development of human functional brain networks. Neuron 67 (5), 735–748.

Pruim, R.H.R., Mennes, M., van Rooij, D., Llera, A., Buitelaar, J.K., Beckmann, C.F., 2015. ICA-AROMA: A robust ICA-based strategy for removing motion artifacts from fMRI data. NeuroImage 112, 267–277. https://doi.org/10.1016/j.neuroimage.2015.02.064.

Pruim, R.H.R., Mennes, M., Buitelaar, J.K., Beckmann, C.F., 2015. Evaluation of ICA-AROMA and alternative strategies for motion artifact removal in resting state fMRI. NeuroImage 112, 278–287. https://doi.org/10.1016/j.neuroimage.2015.02.063.

Roelfs, D., Alnæs, D., Frei, O., van der Meer, D., Smeland, O.B., Andreassen, O.A., Westlye, L.T., Kaufmann, T., 2021. Phenotypically independent profiles relevant to mental health are genetically correlated. Transl. Psychiatry 11 (1), 202. https://doi.org/10.1038/s41398-021-01313-x.

Ronald, A. (2019). Editorial: The psychopathology p factor: will it revolutionise the science and practice of child and adolescent psychiatry? [https://doi.org/10.1111/jcpp.13063]. *Journal of Child Psychology and Psychiatry*, *60*(5), 497–499. https://doi.org/https://doi.org/10.1111/jcpp.13063.

Rubinov, M., Sporns, O., 2010. Complex network measures of brain connectivity: uses and interpretations. NeuroImage 52 (3), 1059–1069.

Sala-Llonch, R., Smith, S.M., Woolrich, M., Duff, E.P., 2019. Spatial parcellations, spectral filtering, and connectivity measures in fMRI: Optimizing for discrimination. Hum. Brain Mapp. 40 (2), 407–419.

Salimi-Khorshidi, G., Douaud, G., Beckmann, C.F., Glasser, M.F., Griffanti, L., Smith, S. M., 2014. Automatic denoising of functional MRI data: combining independent component analysis and hierarchical fusion of classifiers. NeuroImage 90, 449–468. https://doi.org/10.1016/j.neuroimage.2013.11.046.

Sato, J.R., Biazoli, C.E., Salum, G.A., Gadelha, A., Crossley, N., Vieira, G., Zugman, A., Picon, F.A., Pan, P.M., Hoexter, M.Q., Amaro, E., Anés, M., Moura, L.M., Del'Aquilla, M.A.G., McGuire, P., Rohde, L.A., Miguel, E.C., Jackowski, A.P., Bressan, R.A., 2018. Association between abnormal brain functional connectivity in children and psychopathology: a study based on graph theory and machine learning. World J. Biol. Psychiatry 19 (2), 119–129. https://doi.org/10.1080/15622975.2016.1274050.

Schaefer, A., Kong, R., Gordon, E.M., Laumann, T.O., Zuo, X.-N., Holmes, A.J., Eickhoff, S.B., Yeo, B.T.T., 2018. Local-global parcellation of the human cerebral cortex from intrinsic functional connectivity MRI. Cereb. Cortex 28 (9), 3095–3114. https://doi.org/10.1093/cercor/bhx179.

Sha, Z., Wager, T.D., Mechelli, A., He, Y., 2019. Common dysfunction of large-scale neurocognitive networks across psychiatric disorders. Biol. Psychiatry 85 (5), 379–388. https://doi.org/10.1016/j.biopsych.2018.11.011.

Shirer, W.R., Jiang, H., Price, C.M., Ng, B., Greicius, M.D., 2015. Optimization of rs-fMRI pre-processing for enhanced signal-noise separation, test-retest reliability, and group discrimination. NeuroImage 117, 67–79.

Sydnor, V.J., Larsen, B., Bassett, D.S., Alexander-Bloch, A., Fair, D.A., Liston, C., Mackey, A.P., Milham, M.P., Pines, A., Roalf, D.R., 2021. Neurodevelopment of the association cortices: Patterns, mechanisms, and implications for psychopathology. Neuron 109 (18), 2820–2846.

Uddin, M.N., Figley, T.D., Solar, K.G., Shatil, A.S., Figley, C.R., 2019. Comparisons between multi-component myelin water fraction, T1w/T2w ratio, and diffusion tensor imaging measures in healthy human brain structures. Sci. Rep. 9 (1), 1–17.

Vanes, L.D., Dolan, R.J., 2021. Transdiagnostic neuroimaging markers of psychiatric risk: a narrative review. NeuroImage: Clin. 30, 102634 https://doi.org/10.1016/j.nicl.2021.102634.

Voldsbekk, I., Kjelkenes, R., Wolfers, T., Dahl, A., Lund, M.J., Kaufmann, T., Fernandez-Cabello, S., de Lange, A.-M.G., Tamnes, C.K., Andreassen, O.A., Westlye, L.T., Alnæs, D., 2023. Shared pattern of impaired social communication and cognitive ability in the youth brain across diagnostic boundaries. Dev. Cogn. Neurosci. 60, 101219 https://doi.org/10.1016/j.dcn.2023.101219.

Woolrich, M.W., Ripley, B.D., Brady, M., Smith, S.M., 2001. Temporal Autocorrelation in Univariate Linear Modeling of FMRI Data. NeuroImage 14 (6), 1370–1386. https://doi.org/10.1006/nimg.2001.0931.

Xia, C.H., Ma, Z., Ciric, R., Gu, S., Betzel, R.F., Kaczkurkin, A.N., Calkins, M.E., Cook, P. A., García de la Garza, A., Vandekar, S.N., Cui, Z., Moore, T.M., Roalf, D.R., Ruparel, K., Wolf, D.H., Davatzikos, C., Gur, R.C., Gur, R.E., Shinohara, R.T., Bassett, D.S., Satterthwaite, T.D., 2018. Linked dimensions of psychopathology and connectivity in functional brain networks. Nat. Commun. 9 (1), 3003. https://doi.org/10.1038/s41467-018-05317-y.

Xia, M., Wang, J., He, Y., 2013. BrainNet Viewer: A Network Visualization Tool for Human Brain Connectomics. PLoS ONE 8 (7), e68910. https://doi.org/10.1371/journal.pone.0068910.

III

Testing the sensitivity of diagnosis-derived patterns in functional brain networks to symptom burden in a Norwegian youth sample

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Abstract

Aberrant brain network development represents a putative key aetiological component in mental disorders, which typically emerge during childhood and adolescence. Previous resting-state functional MRI studies have identified brain connectivity patterns reflecting psychopathology, but the generalisability to other samples and politico-cultural contexts has not been established.

We investigated whether a previously identified cross-diagnostic case-control and ASD-specific pattern of resting state functional connectivity (discovery sample; children and adolescents aged 5-21 from New York City, USA; n = 1666) would replicate in a Norwegian convenience-based sample of youth (validation sample; children and adolescents aged 9-25 from Oslo, Norway; n = 531). As a test of generalisability, we investigated if these diagnosis-derived RSFC patterns were sensitive to levels of symptom burden in both samples, based on an independent measure of symptom burden (i.e., not diagnostic criteria).

Both the cross-diagnostic and ASD-specific functional connectivity pattern was replicated across samples. Connectivity patterns were significantly associated with thematically appropriate symptom dimensions in the discovery sample. In the validation sample, the ASD-specific functional connectivity pattern showed a weak, inverse relationship with symptoms of conduct problems, hyperactivity, and prosociality, while the cross-diagnostic pattern was not significantly linked to symptoms.

Diagnosis-derived connectivity patterns in a developmental clinical US sample are replicable in a convenience sample of Norwegian youth, however, they were not predictive of mental health symptoms.

1 Introduction

Childhood and adolescence constitute periods of life characterised by substantial developmental adaptations. These include rapid physical, hormonal, brain, cognitive, and psychological changes, adapted to the increasing complexity of our social environment and expectations with age. For example, during this time, the functional networks of the brain undergo large-scale reorganisation and maturation (Paus et al., 2008; Power et al., 2010; Sydnor et al., 2021). Adolescence is also a period with a marked increase in the incidence of psychopathology (Kessler et al., 2007). The co-occurrence of these phenomena has led to the hypothesis that increased brain plasticity during this period results in increased susceptibility to mental illness (Paus et al., 2008). Several studies have identified plausible links between psychopathology in youth and resting-state functional connectivity (RSFC) derived from functional magnetic resonance imaging (fMRI). However, the generalisability of such network patterns to vulnerability for mental illness in non-clinical samples is currently not well demonstrated.

In the context of generalisability and vulnerability, a related question is whether RSFC patterns are specific to diagnostic categories of mental disorders or shared across disorders. Considerable effort has been made to characterise RSFC patterns associated with both diagnostic syndromes and dimensional symptom scores. Transdiagnostic patterns can be identified by including participants with a range of (comorbid) diagnoses, or by modelling dimensional scores of multiple symptom domains. Using these approaches, an increasing number of studies have reported that RSFC patterns relating to psychopathology are transdiagnostic or shared across disorders (Elliott et al., 2018; Karcher et al., 2021; Kebets et al., 2023; Lees et al., 2021; Linke et al., 2021; McTeague et al., 2017; McTeague et al., 2020; Sha et al., 2019; Voldsbekk et al., 2023; Xia et al., 2018). For example, in a population-based sample of children (Adolescent Brain Cognitive Development cohort; ABCD), a shared psychopathology factor was derived and linked to RSFC using both symptom data (Karcher et al., 2021) and diagnostic data (Lees et al., 2021).

The convergence of studies on a shared factor across disorders from studies using both symptom scores as well as binary diagnosis information supports the notion of a latent vulnerability factor on which the diagnostic categories represent extremes (Sprooten et al., 2022). The above-mentioned findings linking a shared latent mental illness factor to brain measures are promising with regard to detecting neural signatures of psychopathology risk in the youth brain. However, an important question is whether these clinical RSFC patterns are sensitive to symptom burden and by extension putative risk in youth samples that are not enriched with mental disorder diagnoses.

Recently, we estimated both diagnosis-specific and cross-diagnostic RSFC patterns in a clinical developmental sample. We identified a pattern specific to a diagnosis of autism spectrum disorder (ASD), as well as a shared patterns across attention-deficit hyperactivity disorder (ADHD), ASD, other neurodevelopmental disorders, anxiety, mood-disorders, and other diagnoses versus no diagnosis (Voldsbekk et al., 2023). In the current study we aimed to investigate whether these diagnosis-derived RSFC patterns are sensitive to mental health symptoms in a Norwegian convenience-based sample of youth. To do this, we investigated whether a) the cross-diagnostic and ASD-specific RSFC patterns previously identified could be replicated in the validation sample, and b) if these RSFC patterns could predict levels of

symptom burden in the validation sample. As a further test of external validity, we also tested whether c) the RSFC patterns previously identified could predict levels of symptom burden in the discovery sample.

2 Material and Methods

2.1 Samples

2.1.1 Discovery sample - HBN

Children and adolescents from New York City, USA were recruited to be part of the HBN cohort (Alexander et al., 2017). The majority have a least one diagnosed mental disorder. In the previous study (Voldsbekk et al., 2023), 1880 participants in HBN took part. 1689 of these were in the discovery sample. Of these, 1666 had available symptom score data used for the current investigation. Missing values in the symptom data were imputed with knnimpute in MATLAB (MathWorks, 2020). For more details regarding MRI data cleaning and quality assurance steps, see Voldsbekk et al. (2023). The final sample consisted of 1666 participants (641 females, mean ± sd age: 10.91 ± 3.14, range: 5-21). See Figure 1 for distributions of sample characteristics.

2.1.2 Validation sample – Brainmint

Children and adolescents in the Oslo region were recruited to participate in the Brains and minds in transition (Brainmint) study. Participants were recruited through convenience sampling by advertising in social media, aiming to recruit young people from the general population interested in contributing to a study investigating brain development and mental health. All participants provided written informed consent prior to their participation in the study. For participants under the age of 16, both parents/legal guardians provided written informed consent on their behalf. Per May 4th 2023, 759 participants had undergone magnetic resonance imaging (MRI) and 697 had responded to questionnaires. Of these, 531 had available both fMRI and symptom score data. No participants had missing data and so all were included in the sample used for the current analysis (390 females, mean ± sd age: 17.69 ± 2.83, range: 9-25). See Figure 1 for distributions of sample characteristics.

2.2 Mental health measures

In the previous study (Voldsbekk et al., 2023), we investigated diagnosis-derived patterns of RSFC in HBN (discovery sample). Diagnostic information was collected using a computerised version of the Schedule for Affective Disorders and Schizophrenia – Children´s version (KSADS) (Kaufman et al., 1997), which is a clinician-administered semi-structured psychiatric interview based on DSM-5. We then labelled diagnoses as belonging to either of these categories: “ADHD”, “ASD”, “anxiety disorders”, “mood disorders”, “other neurodevelopmental disorders”, “other disorders” or “no diagnosis”.

For testing the external validity and predictive utility of diagnosis-derived RSFC patterns, the current study obtained HBN symptom scores from the Strength and Difficulties Questionnaire (Goodman, 1997), which is a 25-item questionnaire measuring emotional and behavioural problems. The SDQ has five syndrome measures: emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, and prosocial behaviour. For this analysis, we used only the summary syndrome measures. In HBN, the SDQ items were

parent-reported. See Figure S1 for symptom load distributions on SDQ summary measures across diagnostic categories in HBN.

Symptom scores in Brainmint were investigated using the same approach as in HBM, only in this sample the SDQ responses were self-reported.

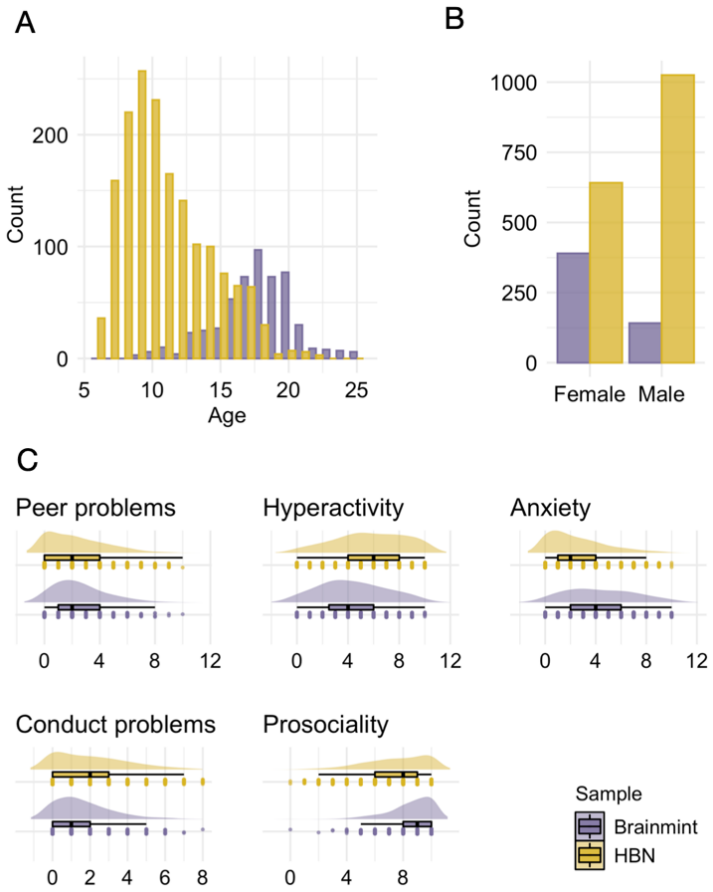

Figure 1. Sample distributions. **A.** Age. **B.** Sex. **C.** SDQ summary syndrome scores. HBN; Healthy brain network sample. Brainmint; Brains and minds in transition sample. SDQ; Strengths and difficulties questionnaire.

2.3 MRI acquisition

HBN MRI data were acquired at four different sites: a mobile scanner at Staten Island (SI), Rutgers University Brain Imaging Centre, Citigroup Biomedical Imaging Centre (CBIC) and Harlem CUNY Advanced Science Research Centre. A detailed overview of the MRI protocol is available elsewhere (http://fcon_1000.projects.nitrc.org/indi/cmi_healthy_brain_network/MRI%20Protocol.html).

Brainmint MRI data were acquired at Oslo University Hospital Ullevål, using a 3.0 T GE SIGNA Premier scanner using a 48-channel head coil. Structural MRI data was acquired using an T_1-weighted MPRAGE sequence (repetition time (TR): 2.526 s, echo time (TE): 2.836 ms, flip angle (FA): 8°, field of view (FOV): 256 mm, slice thickness: 1.0 mm, number of slices: 1). Resting-state functional MRI (rs-fMRI) data was acquired using a T2*-weighted blood-oxygen-level-dependent echo-planar imaging (EPI) sequence with a TR of 800 ms, TE

of 30 ms, multiband acceleration factor = 6, number of slices: 60, 750 repetitions and voxel size = 2.4 × 2.4 × 2.4 mm.

2.4 MRI pre-processing

Rs-fMRI images in HBN were processed with the following pipeline. First, FSL MCFLIRT (Jenkinson et al., 2002) was applied for motion correction, high-pass temporal filtering, spatial smoothing and distortion correction. The rs-fMRI images were registered to a T1-weighted structural image using FLIRT (Jenkinson et al., 2002) and boundary-based registration (Greve & Fischl, 2009). Next, for additional removal of artefacts and noise, we performed non-aggressive ICA-AROMA (Pruim, Mennes, Buitelaar, et al., 2015; Pruim, Mennes, van Rooij, et al., 2015) and FIX (Griffanti et al., 2014; Salimi-Khorshidi et al., 2014). Estimations of temporal signal-to-noise ratio (tSNR) and mean framewise displacement (FD) were calculated by MRIQC (Esteban et al., 2017) and used as covariates in subsequent analyses. For more details, see our previous study (Voldsbekk et al., 2023).

In Brainmint, preprocessing of rs-fMRI images were run using fMRIPrep v22.0.1 (Esteban et al., 2019), an automated pipeline consisting of head motion correction, high-pass temporal filtering, spatial smoothing and distortion correction using MCFLIRT, slice-timing correction using 3dTshift from AFNI, registration to structural reference image using FLIRT and boundary-based registration, and, finally, non-aggressive ICA-AROMA. Same as for HBN, estimations of tSNR and FD were calculated by MRIQC (Esteban et al., 2017).

2.5 Network analysis

RSFC in HBN were derived using the Schaefer parcellation with 100 parcels and 7 networks (Schaefer et al., 2018). These networks include visual A, visual B, visual C, auditory, somatomotor A, somatomotor B, language, salience A, salience B, control A, control B, control C, default A, default B, default C, dorsal attention A and dorsal attention B. The connectivity matrix was then estimated as the L2-norm ridge regression partial correlation between parcel timeseries using FSLNets (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLNets), as implemented in MATLAB (MathWorks, 2020). This resulted in 4950 unique partial correlations (i.e., edges).

RSFC in Brainmint were derived using the same approach as in HBN, making the edges comparable.

2.6 Out-of-sample validation

In the previous work (Voldsbekk et al., 2023), we used partial least squares (PLS) (Krishnan et al., 2011) to identify diagnosis-derived patterns of RSFC, controlling for other diagnosis categories using contrasts. This analysis revealed an ASD-specific pattern, as well as a cross diagnostic case-control pattern.

2.6.1 Testing the replicability of the HBN-derived brain pattern to Brainmint

See Figure 2 for an overview of the out-of-sample validation pipeline. First, we decomposed the Brainmint RSFC data by multiplying them with the brain weights estimated in the HBN PLS analysis. These Brainmint brain weights were then correlated with the original Brainmint RSFC data to get Brainmint connectivity loadings. Then, to assess whether the

brain pattern was replicated across the two samples, we correlated the Brainmint connectivity loadings with HBN connectivity loadings for each latent variable (LV) using Pearson's correlation. Their significance was tested using permutations (n=1000), randomly shuffling the rows (participants) of the Brainmint RSFC data. We calculated *p*-values by dividing the count of permuted maximum R values (including the observed non-permuted value) ≥ the non-permuted R values by the number of permutations. Prior to analysis, Brainmint RSFC data was adjusted for age, sex, tSNR and FD, same as HBN RSFC data prior to running PLS. As a proxy for significance, connectivity loadings were thresholded at Z-scores<|3| in visualisations, akin to the procedure in our previous work using PLS.

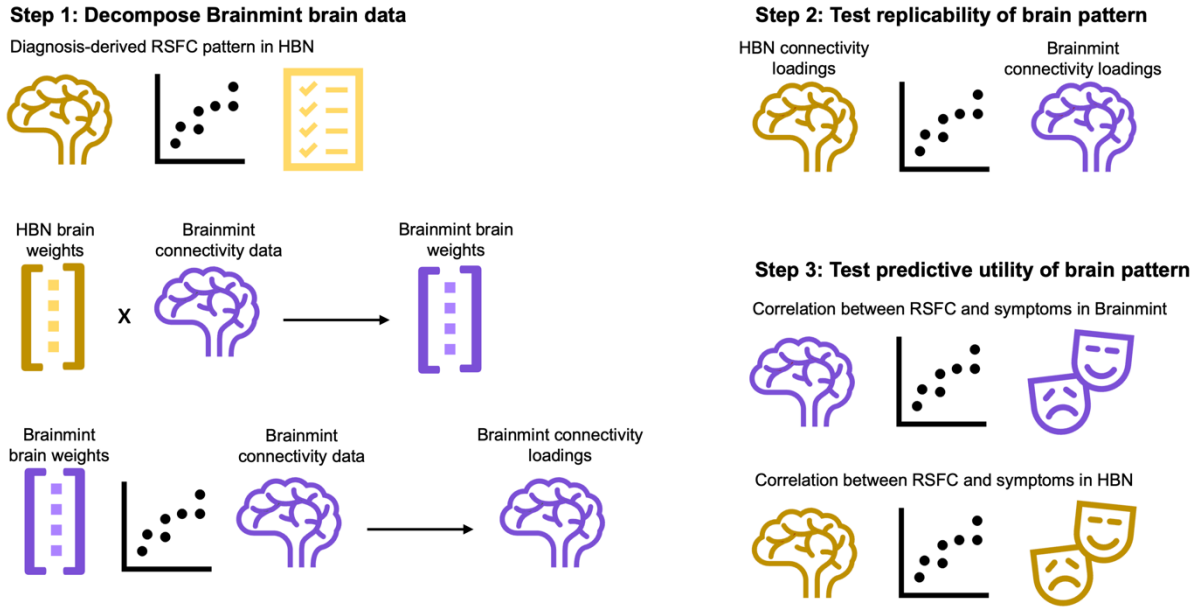

Figure 2. An overview of the out-of-sample validation pipeline. RSFC; resting-state functional connectivity. HBN; Healthy brain network sample. Brainmint; Brains and minds in transition sample.

2.6.2 Testing the predictive utility of the brain pattern

To assess whether the brain pattern had predictive utility, we correlated the derived Brainmint RSFC pattern with Brainmint symptom data. Specifically, we investigated the Spearman's rank correlation between diagnosis-derived brain weights and symptom dimensions from SDQ. To assess the reliability of the associations between brain weights and symptom dimensions, we ran 1000 bootstraps using resampling with replacement. Finally, as a test of external validity, we also ran these correlations between the HBN RSFC pattern and SDQ symptom dimensions in HBN.

3 Results

The correlation between Brainmint and HBN connectivity loadings was significant for both the cross-diagnostic pattern (r=.39, permuted *p*<.001; see Figure 3A) and ASD (r=.49, permuted *p*<.001; see Figure 4A), indicating that both brain patterns were replicable across samples. As shown in Figure 3B, the cross-diagnostic RSFC pattern implicated weaker connectivity within the control network, in addition to weaker between-network connectivity

between the salience network and control network, as well as between the default mode network (DMN) and limbic network. In terms of symptom dimensions, this connectivity pattern exhibited significant positive associations with anxiety, conduct problems, hyperactivity, and peer problems in HBN, as well as a negative association with prosocial behaviour (see Figure 3C). In Brainmint, there were no significant associations between the cross-diagnostic connectivity pattern and symptom dimensions (see Figure 3D).

As shown in Figure 4B, the RSFC pattern for ASD implicated weaker within-network connectivity in the somatomotor network, dorsal attention (DA) network, salience network and DMN. In terms of symptom dimensions, this RSFC pattern was significantly associated with more symptoms of peer problems and hyperactivity in HBN, as well as lower degree of conduct problems and prosociality (see Figure 4C). In Brainmint, the ASD-specific RSFC pattern was associated with higher levels of prosocial behaviour and fewer symptoms of hyperactivity and conduct problems (see Figure 4D).

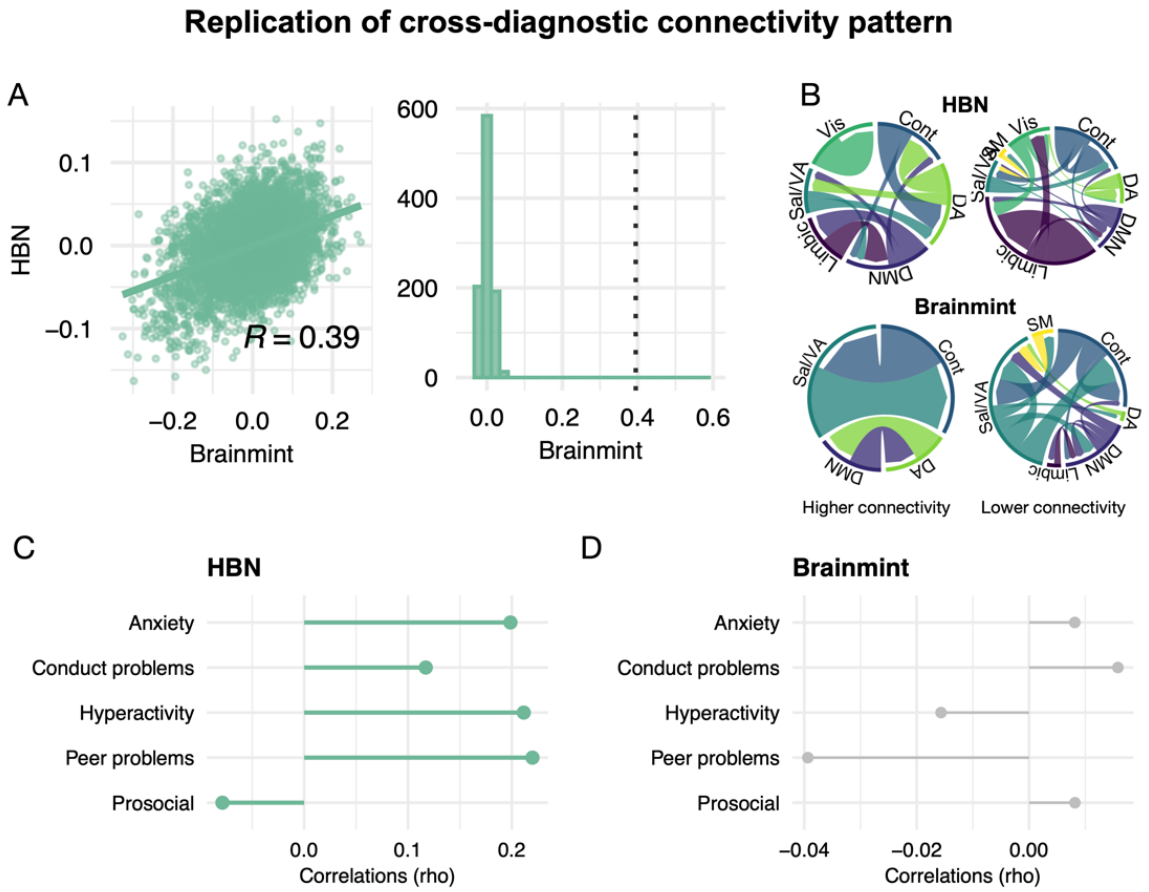

Figure 3. Replication of the cross-diagnostic connectivity pattern from HBN to Brainmint. **A.** Pearson's correlation of connectivity weights between samples (left) and corresponding permutation test (right). The dotted line marks the non-permuted R value. **B.** Visualisation of RSFC pattern in each sample. Depicted are thresholded edges (Z-scores<|3|). **C.** Associations between derived brain pattern and SDQ symptom dimensions in Brainmint. **D.** Associations between derived brain pattern and SDQ symptom dimensions in HBN. Associations with symptom dimensions are marked in bold green if 95% confidence interval of the bootstrap distribution did not contain zero. ASD; Autism spectrum disorder. HBN; Healthy brain network sample. Brainmint; Brains and minds in transition sample. SDQ; strength and difficulties questionnaire.

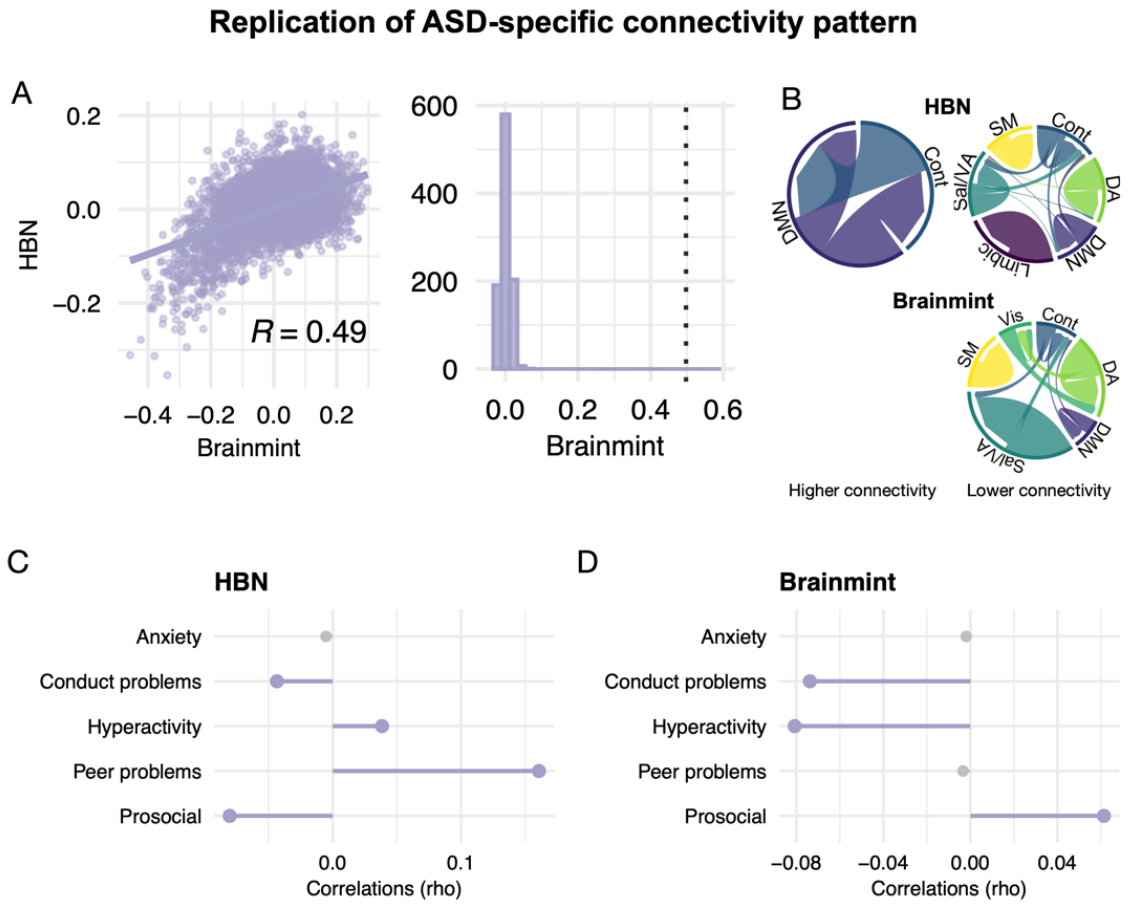

Figure 4. Replication of the ASD-specific connectivity pattern from HBN to Brainmint. **A.** Pearson's correlation of connectivity weights between samples (left) and corresponding permutation test (right). The dotted line marks the non-permuted R value. **B.** Visualisation of RSFC pattern in each sample. Depicted are thresholded edges. **C.** Associations between derived brain pattern and SDQ symptom dimensions in Brainmint. **D.** Associations between derived brain pattern and SDQ symptom dimensions in HBN. Associations with symptom dimensions are marked in bold purple if 95% confidence interval of the bootstrap distribution did not contain zero. ASD; Autism spectrum disorder. HBN; Healthy brain network sample. Brainmint; Brains and minds in transition sample. SDQ; strength and difficulties questionnaire.

4 Discussion

The current study aimed to investigate whether psychopathology-related RSFC patterns are informative of vulnerability for mental illness in undiagnosed individuals by replicating connectivity patterns derived in a developmental clinical sample from the US in a Norwegian convenience-based sample of youth. However, the RSFC pattern was only sensitive to symptom burden in the discovery sample. Specifically, we found that the RSFC patterns were associated with symptom dimensions thematically overlapping with core symptom characteristics in the discovery sample, while in the validation sample we found a weak, inverse relationship for ASD. This latter association was small, hence exhibiting low predictive utility at the individual level. Taken together, these results show that although diagnosis-derived RSFC patterns replicate across samples, their utility is greatly limited due to their lack of sensitivity to symptom burden.

Replicability and generalisability of neuroimaging findings remain a challenge in the field (Botvinik-Nezer & Wager, 2022). Historically, small sample sizes and lack of methodological rigour have resulted in poor replication rates, possibly reflecting that many published findings are potential false positives (Ioannidis, 2005). To overcome such challenges, increasing effort has been put into developing procedures for reproducible science (Niso et al., 2022). With the advent of multivariate machine learning approaches in neuroscience, issues related to statistical power and extensive univariate testing in small samples have been improved (Botvinik-Nezer & Wager, 2022). However, these multivariate approaches come with new challenges, such as data leakage, overfitting and the need for sufficiently large data sets to ensure robustness (Botvinik-Nezer & Wager, 2022; Davatzikos, 2019; Poldrack et al., 2020; Varoquaux, 2018). Although the current study aimed to overcome some of these challenges, we still did not obtain generalisable results.

Generalisation of RSFC patterns related to psychopathology has been hampered by challenges related to the stability and reliability of RSFC results, as well as variations in mental health profiles across cohorts (Uddin et al., 2017). Data driven approaches to symptom clustering have to some degree yielded reproducible clusters or hierarchies of symptom structure across samples (Caspi et al., 2014). Recently, we derived brain-based latent dimensions of psychopathology using symptom covariance with functional brain networks in HBN (Voldsbekk et al., 2023). Similar brain-based dimensions of psychopathology were identified in ABCD, combining measures of both brain structure and RSFC (Kebets et al., 2023). By decomposing the HBN data using feature weights estimated in ABCD from Kebets et al., we found that the symptom dimensions replicated, however the RSFC patterns did not (Voldsbekk et al., 2023). Previous attempts at replication of brain-symptom mapping in independent samples have shown similar findings of replicating latent clinical dimensions, but weak or non-replicable RSFC patterns (Linke et al., 2021). In light of this, it is surprising that the current study could replicate case-control and ASD-specific RSFC patterns from HBN to Brainmint. Even so, the clinical associations of this pattern in the discovery sample were not replicated in the validation sample.

The current replication effort is conducted across two widely different samples, both in terms of age, sex distribution, and other demographical variables, and in their mental health profile. While the HBN sample consists of mainly children with diagnosed neurodevelopmental disorders, the Brainmint sample consists of adolescents recruited from the community. Some of these adolescents have elevated symptom burden and may meet the diagnostic criteria of a mental disorder, but this sample is not enriched with diagnoses as is the case with HBN. The symptom distribution is also different, with higher prevalence of anxiety symptoms in Brainmint, as compared to conduct problems and peer problems in HBN. In line with this, there is also a marked difference in the sex distribution across the two samples, with higher prevalence of males in HBN and the majority being female in Brainmint. Given these differences, it is all the more striking that the RSFC patterns replicated. Concomitantly, this may also explain the lack of replicable clinical associations. One possible explanation could be that the RSFC patterns do reflect some vulnerability to psychopathology, only it is not sensitive enough to be predictive in a widely different sample.

Consistent with the symptom load distribution in HBN across diagnostic categories, the RSFC pattern in HBN picked up associations with peer problems, hyperactivity, and

prosocial behaviour for the ASD-specific pattern and all symptom dimensions for the cross-diagnostic pattern. This represents a sanity check that the diagnosis-derived RSFC pattern in HBN picks up similar associations with symptom load as the diagnosis groups they are modelled to represent. Reliability of mental health measures has remained a challenge in the field (Nikolaidis et al., 2022). Here we show that RSFC patterns derived from diagnostic information exhibit associations with an independent measurement of symptom load that are overlapping with symptom load associations observed for each diagnostic category. This supports that these RSFC patterns reflect something that overlaps with their corresponding diagnostic categories. However, this sensitivity of the RSFC pattern was not generalisable to Brainmint. The RSFC pattern in Brainmint picked up an inverse relationship with prosocial behaviour, hyperactivity, and conduct problems for the ASD-specific pattern, indicating that higher prosociality and lower conduct problems and hyperactivity was associated with a more "ASD-like" brain pattern. This finding is paradoxical and the opposite of what one would expect. While it is too early to conclude based on one preliminary association only, it is worth noting that the strength of this association was low. Similarly, there was no significant associations with the cross-diagnostic pattern in Brainmint. Given these weak group-level associations, with low predictive utility at the individual level, adding too much emphasis to this preliminary finding is unwarranted. Instead, this result adheres to the previous literature finding generalisation of RSFC results a challenge (Uddin et al., 2017).

Some further limitations should be noted. First, RSFC results are influenced by methodological choices (Sala-Llonch et al., 2019; Shirer et al., 2015). To increase reproducibility of RSFC networks, we utilised an established parcellation scheme (Schaefer et al., 2018). Second, the two samples underwent slightly differing fMRI preprocessing pipelines. However, this difference should diminish, rather than inflate, any reproducibility of the findings across samples. Third, the symptom dimensions from SDQ were measured by parent-report in HBN and by self-report in Brainmint. This may have induced systematic variations in the data across the two samples due to differences in response style, which may explain why the community-based sample seemed to exhibit a higher symptom burden than the clinical sample. This limitation represents an important reminder that low reliability in mental health measures impedes scientific discovery (Nikolaidis et al., 2022) and underscores that the current results must be interpreted with caution.

5 Conclusions

This work demonstrates that diagnosis-derived RSFC patterns in a US developmental clinical sample can be extended to a Norwegian convenience-based sample of youth. Both the cross-diagnostic and the ASD-specific RSFC patterns were found to replicate across samples. However, although both connectivity patterns exhibited significant associations with thematically appropriate symptom dimensions in both the discovery sample (HBN), they were not found to be sensitive to overlapping dimensions of symptom burden in the validation sample (Brainmint). Implications of this work is that generalisation of RSFC results remains a challenge. For any psychopathology-related RSFC patterns to be generalisable and clinically relevant, their sensitivity to symptom burden across samples represents a prerequisite.

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References

Alexander, L. M., Escalera, J., Ai, L., Andreotti, C., Febre, K., Mangone, A., Vega-Potler, N., Langer, N., Alexander, A., & Kovacs, M. (2017). An open resource for transdiagnostic research in pediatric mental health and learning disorders. *Scientific data*, *4*(1), 1-26.

Botvinik-Nezer, R., & Wager, T. D. (2022). Reproducibility in Neuroimaging Analysis: Challenges and Solutions. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*. https://doi.org/https://doi.org/10.1016/j.bpsc.2022.12.006

Caspi, A., Houts, R. M., Belsky, D. W., Goldman-Mellor, S. J., Harrington, H., Israel, S., Meier, M. H., Ramrakha, S., Shalev, I., Poulton, R., & Moffitt, T. E. (2014). The p Factor: One General Psychopathology Factor in the Structure of Psychiatric Disorders? *Clin Psychol Sci*, *2*(2), 119-137. https://doi.org/10.1177/2167702613497473

Davatzikos, C. (2019). Machine learning in neuroimaging: Progress and challenges. *NeuroImage*, *197*, 652.

Elliott, M. L., Romer, A., Knodt, A. R., & Hariri, A. R. (2018). A Connectome-wide Functional Signature of Transdiagnostic Risk for Mental Illness. *Biological Psychiatry*, *84*(6), 452-459. https://doi.org/https://doi.org/10.1016/j.biopsych.2018.03.012

Esteban, O., Birman, D., Schaer, M., Koyejo, O. O., Poldrack, R. A., & Gorgolewski, K. J. (2017). MRIQC: Advancing the automatic prediction of image quality in MRI from unseen sites. *PLoS ONE*, *12*(9), e0184661. https://doi.org/10.1371/journal.pone.0184661

Esteban, O., Markiewicz, C. J., Blair, R. W., Moodie, C. A., Isik, A. I., Erramuzpe, A., Kent, J. D., Goncalves, M., DuPre, E., & Snyder, M. (2019). fMRIPrep: a robust preprocessing pipeline for functional MRI. *Nature methods*, *16*(1), 111-116.

Goodman, R. (1997). The Strengths and Difficulties Questionnaire: a research note. *Journal of Child Psychology and Psychiatry*, *38*(5), 581-586.

Greve, D. N., & Fischl, B. (2009). Accurate and robust brain image alignment using boundary-based registration. *Neuroimage*, *48*(1), 63-72. https://doi.org/https://doi.org/10.1016/j.neuroimage.2009.06.060

Griffanti, L., Salimi-Khorshidi, G., Beckmann, C. F., Auerbach, E. J., Douaud, G., Sexton, C. E., Zsoldos, E., Ebmeier, K. P., Filippini, N., Mackay, C. E., Moeller, S., Xu, J., Yacoub, E., Baselli, G., Ugurbil, K., Miller, K. L., & Smith, S. M. (2014). ICA-based artefact removal and accelerated fMRI acquisition for improved resting state network imaging. *NeuroImage*, *95*, 232-247. https://doi.org/https://doi.org/10.1016/j.neuroimage.2014.03.034

Ioannidis, J. P. (2005). Why most published research findings are false. *PLoS medicine*, *2*(8), e124.

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *NeuroImage*, *17*(2), 825-841. https://doi.org/10.1016/S1053-8119(02)91132-8

Karcher, N. R., Michelini, G., Kotov, R., & Barch, D. M. (2021). Associations Between Resting-State Functional Connectivity and a Hierarchical Dimensional Structure of Psychopathology in Middle Childhood. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *6*(5), 508-517. https://doi.org/https://doi.org/10.1016/j.bpsc.2020.09.008

Kaufman, J., Birmaher, B., Brent, D., Rao, U. M. A., Flynn, C., Moreci, P., Williamson, D., & Ryan, N. (1997). Schedule for Affective Disorders and Schizophrenia for School-

Age Children-Present and Lifetime Version (K-SADS-PL): Initial Reliability and Validity Data. *Journal of the American Academy of Child & Adolescent Psychiatry*, *36*(7), 980-988. https://doi.org/https://doi.org/10.1097/00004583-199707000-00021

Kebets, V., Piguet, C., Chen, J., Ooi, L. Q. R., Kirschner, M., Siffredi, V., Misic, B., Yeo, B. T., & Bernhardt, B. (2023). Multimodal neural correlates of childhood psychopathology. *bioRxiv*, 2023.2003. 2002.530821.

Kessler, R. C., Angermeyer, M., Anthony, J. C., De Graaf, R., Demyttenaere, K., Gasquet, I., De Girolamo, G., Gluzman, S., Gureje, O., & Haro, J. M. (2007). Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. *World psychiatry*, *6*(3), 168.

Krishnan, A., Williams, L. J., McIntosh, A. R., & Abdi, H. (2011). Partial Least Squares (PLS) methods for neuroimaging: A tutorial and review. *NeuroImage*, *56*(2), 455-475. https://doi.org/https://doi.org/10.1016/j.neuroimage.2010.07.034

Lees, B., Squeglia, L. M., McTeague, L. M., Forbes, M. K., Krueger, R. F., Sunderland, M., Baillie, A. J., Koch, F., Teesson, M., & Mewton, L. (2021). Altered Neurocognitive Functional Connectivity and Activation Patterns Underlie Psychopathology in Preadolescence. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *6*(4), 387-398. https://doi.org/https://doi.org/10.1016/j.bpsc.2020.09.007

Linke, J. O., Abend, R., Kircanski, K., Clayton, M., Stavish, C., Benson, B. E., Brotman, M. A., Renaud, O., Smith, S. M., Nichols, T. E., Leibenluft, E., Winkler, A. M., & Pine, D. S. (2021). Shared and Anxiety-Specific Pediatric Psychopathology Dimensions Manifest Distributed Neural Correlates. *Biological Psychiatry*, *89*(6), 579-587. https://doi.org/10.1016/j.biopsych.2020.10.018

MathWorks. (2020). *MATLAB*. In

McTeague, L. M., Huemer, J., Carreon, D. M., Jiang, Y., Eickhoff, S. B., & Etkin, A. (2017). Identification of Common Neural Circuit Disruptions in Cognitive Control Across Psychiatric Disorders. *American Journal of Psychiatry*, *174*(7), 676-685. https://doi.org/10.1176/appi.ajp.2017.16040400

McTeague, L. M., Rosenberg, B. M., Lopez, J. W., Carreon, D. M., Huemer, J., Jiang, Y., Chick, C. F., Eickhoff, S. B., & Etkin, A. (2020). Identification of common neural circuit disruptions in emotional processing across psychiatric disorders. *American Journal of Psychiatry*, *177*(5), 411-421.

Nikolaidis, A., Chen, A. A., He, X., Shinohara, R., Vogelstein, J., Milham, M., & Shou, H. (2022). Suboptimal phenotypic reliability impedes reproducible human neuroscience. *bioRxiv*, 2022.2007. 2022.501193.

Niso, G., Botvinik-Nezer, R., Appelhoff, S., De La Vega, A., Esteban, O., Etzel, J. A., Finc, K., Ganz, M., Gau, R., & Halchenko, Y. O. (2022). Open and reproducible neuroimaging: from study inception to publication. *NeuroImage*, 119623.

Paus, T., Keshavan, M., & Giedd, J. N. (2008). Why do many psychiatric disorders emerge during adolescence? *Nature Reviews Neuroscience*, *9*(12), 947-957. https://www.nature.com/articles/nrn2513.pdf

Poldrack, R. A., Huckins, G., & Varoquaux, G. (2020). Establishment of best practices for evidence for prediction: a review. *JAMA Psychiatry*, *77*(5), 534-540.

Power, J. D., Fair, D. A., Schlaggar, B. L., & Petersen, S. E. (2010). The development of human functional brain networks. *Neuron*, *67*(5), 735-748.

Pruim, R. H. R., Mennes, M., Buitelaar, J. K., & Beckmann, C. F. (2015). Evaluation of ICA-AROMA and alternative strategies for motion artifact removal in resting state fMRI. *NeuroImage*, *112*, 278-287. https://doi.org/https://doi.org/10.1016/j.neuroimage.2015.02.063

Pruim, R. H. R., Mennes, M., van Rooij, D., Llera, A., Buitelaar, J. K., & Beckmann, C. F. (2015). ICA-AROMA: A robust ICA-based strategy for removing motion artifacts from fMRI data. *NeuroImage*, *112*, 267-277. https://doi.org/https://doi.org/10.1016/j.neuroimage.2015.02.064

Sala-Llonch, R., Smith, S. M., Woolrich, M., & Duff, E. P. (2019). Spatial parcellations, spectral filtering, and connectivity measures in fMRI: Optimizing for discrimination. *Human Brain Mapping*, *40*(2), 407-419.

Salimi-Khorshidi, G., Douaud, G., Beckmann, C. F., Glasser, M. F., Griffanti, L., & Smith, S. M. (2014). Automatic denoising of functional MRI data: Combining independent component analysis and hierarchical fusion of classifiers. *NeuroImage*, *90*, 449-468. https://doi.org/https://doi.org/10.1016/j.neuroimage.2013.11.046

Schaefer, A., Kong, R., Gordon, E. M., Laumann, T. O., Zuo, X.-N., Holmes, A. J., Eickhoff, S. B., & Yeo, B. T. T. (2018). Local-Global Parcellation of the Human Cerebral Cortex from Intrinsic Functional Connectivity MRI. *Cerebral Cortex*, *28*(9), 3095-3114. https://doi.org/10.1093/cercor/bhx179

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

Shirer, W. R., Jiang, H., Price, C. M., Ng, B., & Greicius, M. D. (2015). Optimization of rs-fMRI pre-processing for enhanced signal-noise separation, test-retest reliability, and group discrimination. *NeuroImage*, *117*, 67-79.

Sprooten, E., Franke, B., & Greven, C. U. (2022). The P-factor and its genomic and neural equivalents: an integrated perspective. *Molecular Psychiatry*, *27*(1), 38-48.

Sydnor, V. J., Larsen, B., Bassett, D. S., Alexander-Bloch, A., Fair, D. A., Liston, C., Mackey, A. P., Milham, M. P., Pines, A., & Roalf, D. R. (2021). Neurodevelopment of the association cortices: Patterns, mechanisms, and implications for psychopathology. *Neuron*, *109*(18), 2820-2846.

Uddin, L. Q., Dajani, D. R., Voorhies, W., Bednarz, H., & Kana, R. K. (2017). Progress and roadblocks in the search for brain-based biomarkers of autism and attention-deficit/hyperactivity disorder. *Translational Psychiatry*, *7*(8), e1218-e1218. https://doi.org/10.1038/tp.2017.164

Varoquaux, G. (2018). Cross-validation failure: Small sample sizes lead to large error bars. *NeuroImage*, *180*, 68-77.

Voldsbekk, I., Kjelkenes, R., Dahl, A., Holm, M. C., Lund, M. J., Kaufmann, T., Tamnes, C. K., Andreassen, O. A., Westlye, L. T., & Alnæs, D. (2023). Delineating disorder-general and disorder-specific dimensions of psychopathology from functional brain networks in a developmental clinical sample. *Developmental Cognitive Neuroscience*, *62*, 101271. https://doi.org/https://doi.org/10.1016/j.dcn.2023.101271

Xia, C. H., Ma, Z., Ciric, R., Gu, S., Betzel, R. F., Kaczkurkin, A. N., Calkins, M. E., Cook, P. A., García de la Garza, A., Vandekar, S. N., Cui, Z., Moore, T. M., Roalf, D. R., Ruparel, K., Wolf, D. H., Davatzikos, C., Gur, R. C., Gur, R. E., Shinohara, R. T., Bassett, D. S., & Satterthwaite, T. D. (2018). Linked dimensions of psychopathology and connectivity in functional brain networks. *Nature Communications*, *9*(1), 3003. https://doi.org/10.1038/s41467-018-05317-y