Review

Biological Psychiatry

Approaches to Defining Common and Dissociable Neurobiological Deficits Associated With Psychopathology in Youth

Antonia N. Kaczkurkin, Tyler M. Moore, Aristeidis Sotiras, Cedric Huchuan Xia, Russell T. Shinohara, and Theodore D. Satterthwaite

ABSTRACT

Psychiatric disorders show high rates of comorbidity and nonspecificity of presenting clinical symptoms, while demonstrating substantial heterogeneity within diagnostic categories. Notably, many of these psychiatric disorders first manifest in youth. We review progress and next steps in efforts to parse heterogeneity in psychiatric symptoms in youths by identifying abnormalities within neural circuits. To address this fundamental challenge in psychiatry, a number of methods have been proposed. We provide an overview of these methods, broadly organized into dimensional versus categorical approaches and single-view versus multiview approaches. Dimensional approaches including factor analysis and canonical correlation analysis aim to capture dimensional associations between psychopathology and brain measures across a continuous spectrum from health to disease. In contrast, categorical approaches, such as clustering and community detection, aim to identify subtypes of individuals within a class of symptoms or brain features. We highlight several studies that apply these methods to samples of youths and discuss issues to consider when using these approaches. Finally, we end by highlighting avenues for future research.

Keywords: Adolescents, Heterogeneity, Imaging, Neurobiology, Psychopathology, Youth

https://doi.org/10.1016/j.biopsych.2019.12.015

Youth, which we define broadly as childhood, adolescence, and young adulthood, is a period during which many psychiatric disorders first manifest (1,2). It is also a time of marked development in brain structure and function (3,4). Despite dramatic advances in neuroimaging methodology that have made it possible to measure the structure and function of neural circuits, attempts to isolate neurobiological substrates of psychopathology have been hampered by the simultaneous comorbidity among and heterogeneity within psychiatric diagnoses. For example, psychiatric disorders share many presenting clinical symptoms (5), which likely contributes to the apparent nonspecificity of neural mechanisms associated with psychopathology (6–13). At the same time, there is considerable heterogeneity in the presentation of clinical symptoms (14–17). There is increasing interest in understanding clinical heterogeneity in psychopathology in terms of underlying biological mechanisms (18), which may provide the basis for a biologically based nosology for mental disorders. However, thus far, the majority of this work has been restricted to adult samples.

The goal of this review is to introduce different approaches to understanding neurobiological heterogeneity within psychiatric disorders, with a focus on studies using these approaches in samples of youths. Specifically, we concentrate on methods for defining common and dissociable neurobiological deficits associated with psychopathology. Notably, the focus of this review is not on trajectories of developmental change or theoretical nosological debates. See other articles in this special issue for an overview of patterns of brain development using longitudinal studies and for a comprehensive review of issues concerning the bifactor model. Instead, our goal is to introduce the reader to a range of approaches for parsing common and dissociable neurobiological heterogeneity, while highlighting the similarities and differences between the methods. Of note, we focus only on methods that have been applied in samples of youths. While we do not provide a comprehensive tutorial on any particular method, we refer the reader to more detailed presentations of these methods when available. We organize this review according to 2 axes that aim to understand the complex mapping between neural deficits and clinical symptoms: dimensional versus categorical approaches and single-view versus multiview approaches. We begin by defining these 4 broad approaches and then highlight studies that apply these methods to samples of youths. We follow this with a discussion of the issues to consider when using these approaches, and we end by discussing considerations for future research.

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ISSN: 0006-3223

DIMENSIONAL VERSUS CATEGORICAL AND SINGLE-VIEW VERSUS MULTIVIEW APPROACHES

When reviewing methods for parsing heterogeneity, we distinguish between dimensional versus categorical approaches. Here we are referring to whether the approach produces dimensions (continuous variables) or categories (clusters or subtypes) of the measure of interest. Specifically, dimensions represent the loadings onto symptoms, and each individual receives a dimensional score, while categories represent subtypes of people who share features in common, and each individual is classified into a category. Research has shown that many psychiatric symptoms exist on a continuum, with diagnosable psychopathology being an extreme phenotype of variation that is present in the general population (19). Dimensional approaches are able to account for this continuous spectrum from health to disease including subthreshold levels of psychopathology. However, multiple mechanisms may drive the extreme phenotypes of psychopathology, and one can also use categorical approaches to identify subtypes of psychopathology.

A second important distinction is between single-view and multiview methodological approaches. This refers to the nature of the input data, which can be symptoms, brain features, or both. Any type of data can be considered, but we limit our review here to clinical symptoms and neuroimaging measures, given our focus on neurobiological heterogeneity in psychopathology. Single-view approaches consider data from a single feature set (e.g., symptoms). The output can be dimensional (a spectrum of symptoms) or categorical (subtypes of people), but the input reflects a single data type. In contrast, multiview approaches use input data from multiple feature sets, such as integrating both symptoms and brain features (20). Again, the output can be dimensional (continuous dimensions representing combinations of symptoms and brain features) or categorical (subtypes characterized by different combinations of symptoms and brain features). Collectively, we can organize the approaches discussed into this dimensional versus categorical and single-view versus multiview framework.

Single-View Dimensional Approaches

Single-view dimensional approaches take as input a single feature set (clinical symptoms or brain measures) and produce dimensional output. One use of this approach is to reduce a large feature set into a smaller number of latent summary variables for discovery of hidden relationships and/or for data reduction. For example, approaches such as independent component analysis, principal component analysis, and nonnegative matrix factorization can be used to reduce high-dimensional symptoms or brain features into a smaller number of components (21–31). Another common approach involves factor analysis, which summarizes a large number of psychiatric symptoms into latent dimensions that can then be related to various neurobiological measures [T. Moore, Ph.D., *et al.*, unpublished data, 2019; (32–38)]. Two models for this purpose include correlated traits and bifactor models (39). Correlated traits models (e.g., factors from an exploratory factor analysis) produce correlated symptom factors. In contrast, bifactor models reveal a hierarchical structure of symptoms including a general psychopathology (p) factor that represents the overall burden of psychopathology across disorders (Figure 1) (40). Akin to the g factor in general intelligence, the p factor represents the symptoms that psychiatric disorders share in common (41). In addition to the p factor, a bifactor model identifies uncorrelated subfactors of psychopathology, such as factors for internalizing/fear, anxious-misery/distress, externalizing/behavioral, and psychosis/thought disorder (32–38,42).

The p factor has been associated with a number of neurobiological measures in youths, including reduced gray matter volume (22,43), reduced activity in executive regions (44), elevated resting-state cerebral blood flow (45), reduced fractional anisotropy (46), and delay in connectome distinctiveness (Figure 2) (47). In addition, dissociable deficits specific to the symptom domains of fear, anxious-misery/distress, behavioral/externalizing, and psychosis/thought disorder exist. For example, factors related to internalizing symptoms are associated with reduced gray matter volume in specific regions (43), widespread hyperactivation of the executive network (44), reduced cortical thickness (22), and specific abnormalities in cerebral blood flow (45). The bifactor model is useful for summarizing symptoms into dimensions that capture common variance across disorders (p factor) and unique variance within specific classes of symptoms. The studies applying this method to samples of youths and then relating these factors to neuroimaging measures suggest that there may exist both common and dissociable neurobiological substrates of psychopathology in youths.

Multiview Dimensional Approaches

While single-view dimensional approaches consider only a single data type as input, multiview dimensional approaches take as input 2 or more feature sets (symptoms and brain) and produce dimensional summaries of the interrelationships between the feature sets. Two commonly used multiview dimensional methods are partial least squares (PLS) regression and canonical correlation analysis (CCA) (48–51). Both methods seek to find linear combinations of brain features that predict linear combinations of clinical symptoms (Figure 1). A growing number of studies have used PLS regression and CCA to link neurobiological measures to psychopathology in adults (52–66).

In youths, CCA has been used to link functional connectivity patterns to behavioral measures, including demographics, IQ, and a variety of self-report measures (67). However, the participants of this study included healthy youths (n = 281) and a much smaller number of youths with major depression (n = 25); as a result, relatively limited psychopathology was present in participants. It should also be noted that the assumptions of CCA often do not hold in high-dimensional imaging data (68). Alternative methods such as sparse CCA are able to overcome these limitations in high-dimensional data by simplifying the model to avoid overfitting and increase interpretability (69–71). Our group used sparse CCA to link dimensional psychopathology symptoms to functional connectivity measures in a large sample of 663 youths (72). The results revealed that mood, psychosis, fear,

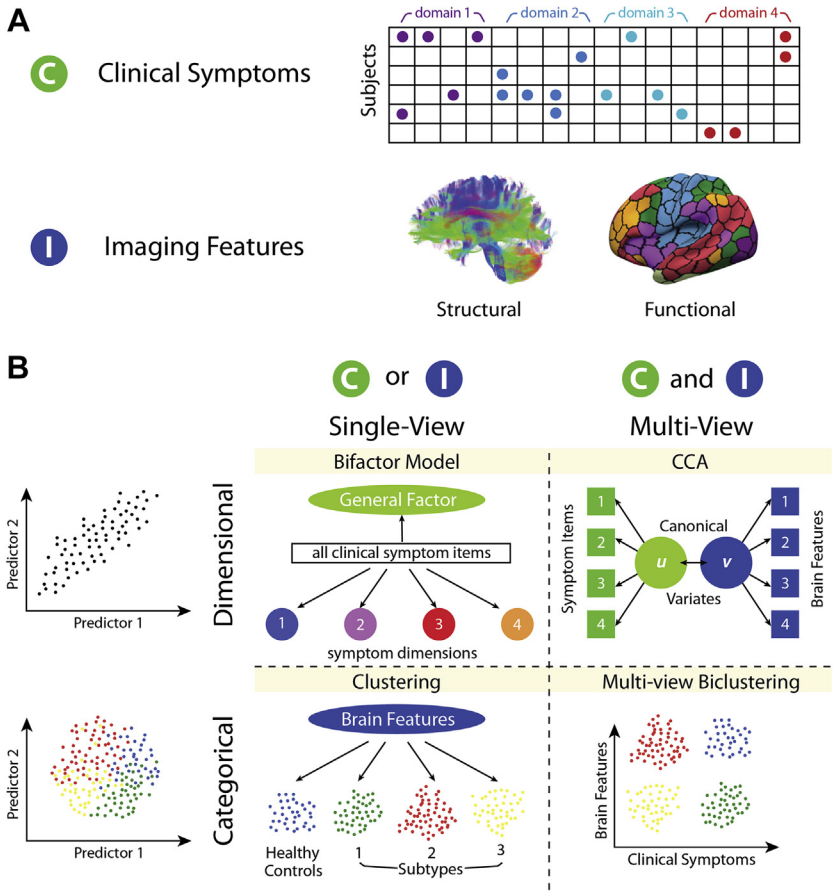


Figure 1. Examples of representative approaches: single-view vs. multiview and dimensional vs. categorical. Schematic illustrating the 4 broad approaches surveyed in this review. **(A)** The input data for each approach may include clinical symptoms, imaging features, or a combination of clinical symptoms and imaging features. **(B)** Each approach is illustrated with an exemplar technique (note that many other methods are available as well). Single-view dimensional approaches (e.g., bifactor model) take as input a single data type, such as clinical symptoms, and output latent dimensions that summarize the data. Multiview dimensional approaches (e.g., canonical correlation analysis [CCA]) take as input 2 data types and identify linear combinations of the 2 types. Single-view categorical approaches (e.g., clustering) find subtypes based on a single feature set. Multiview categorical approaches (e.g., multiview biclustering) find subtypes based on multiple views of the data, where the input is 2 or more feature sets.

and externalizing behavior were associated with distinct patterns of connectivity, while loss of network segregation between the default mode and executive networks was common across these dimensions (Figure 3) (72). Methods such as PLS regression and CCA are useful for measuring brain-behavior relationships. However, relatively few studies have applied these methods in younger populations, suggesting the need for additional studies in samples of youths to replicate these results.

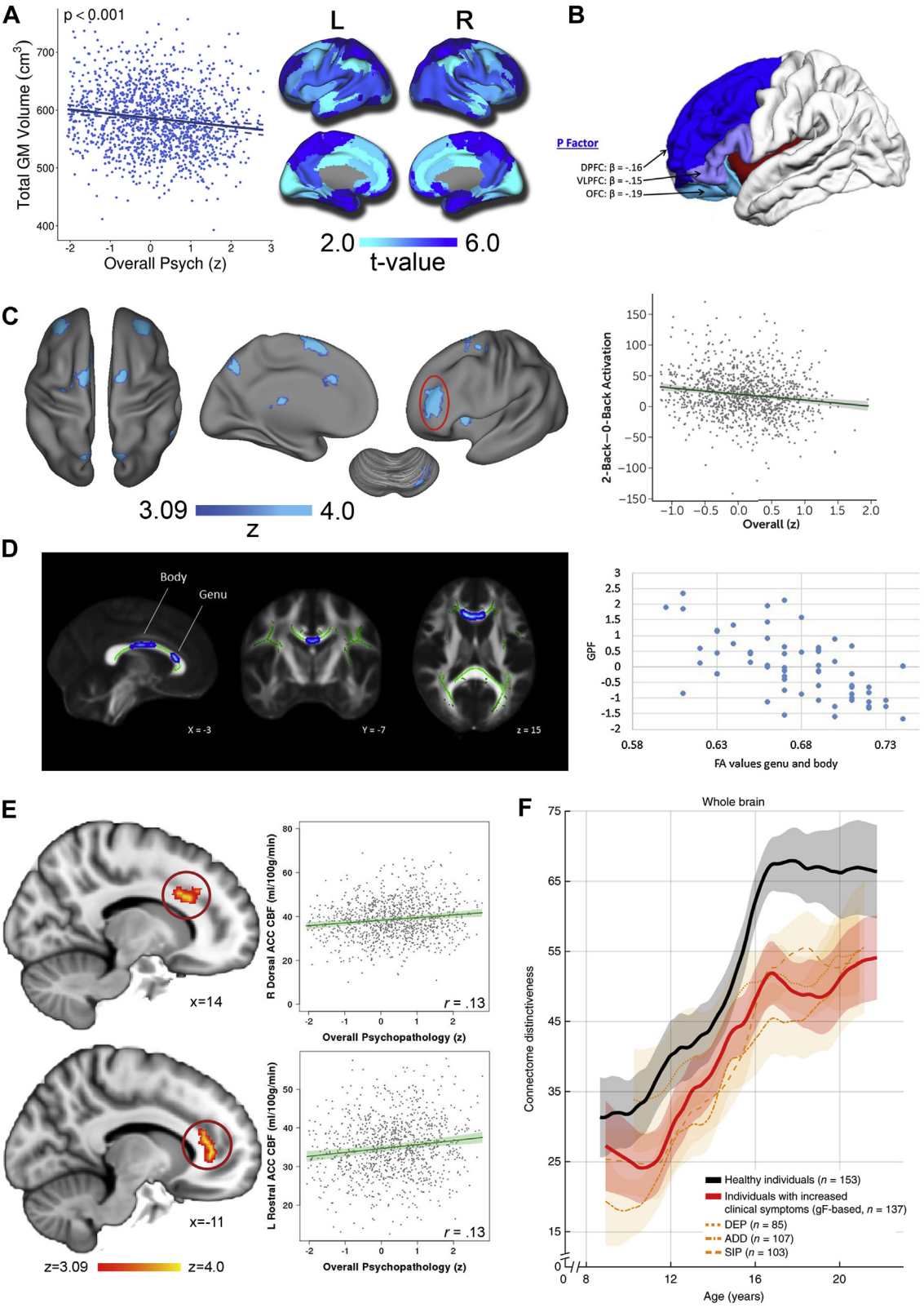
Single-View Categorical Approaches

Single-view categorical approaches take a single modality as input (symptoms or brain features) and produce clusters or subtypes of individuals. Notably, these techniques may also be used to discover clusters of variables; however, here we focus on the use of these methods to reveal clusters of individuals with common features. While many studies have clustered on psychiatric symptoms, behavioral measures, or neuropsychological performance in both adults and youths (73–93), here we focus on studies that cluster based on imaging measures. A number of studies have identified subtypes based on imaging features in adults (60,94–108).

In terms of younger samples, neurobiological subtypes of internalizing/externalizing symptoms have been identified in samples of infants (109). Additionally, community detection has been used to identify subtypes of youths with attention-deficit/hyperactivity disorder using measures of intrinsic functional connectivity (110,111). Our group has used a recently developed machine learning method, HYDRA (94), in 1141 youths to identify 2 subtypes of internalizing youths differentiated by abnormalities in brain structure, function, and white matter integrity, with one subtype showing poorer functioning across multiple domains (Figure 4) (112). In contrast to many clustering approaches, HYDRA accounts for variability in the control group while uncovering subtypes in the symptomatic group. These approaches are potentially useful because they seek to identify subtypes that "carve nature at its joints" based on underlying neurobiology, rather than relying on symptom measures. Studies using this approach in samples of youths are just beginning to emerge.

Multiview Categorical Approaches

Multiview categorical approaches take as input 2 or more feature sets (e.g., symptoms and brain measures) and produce clusters or subtypes characterized by different combinations of those features (20). Biclustering is one method that clusters on both rows (subjects) and columns (features) simultaneously to generate clusters representing subsets of subjects related to subsets of features (113). While still a single-view approach, this method can be adapted to be multiview by including more


A
p < 0.001
Total GM Volume (cm3)
Overall Psych (z)
L
R
2.0
6.0
t-value
B
P Factor
DPFC: β = -.16
VLPFC: β = -.15
OFC: β = -.19
C
3.09
4.0
z
2-Back—0-Back Activation
Overall (z)
D
Body
Genu
X = -3
Y = -7
z = 15
GPF
FA values genu and body
E
x=14
x=-11
z=3.09
z=4.0
R Dorsal ACC CBF (ml/100g/min)
L Rostral ACC CBF (ml/100g/min)
r = .13
Overall Psychopathology (z)
F
Whole brain
Connectome distinctiveness
Age (years)
Healthy individuals (n = 153)
Individuals with increased clinical symptoms (gF-based, n = 137)
DEP (n = 85)
ADD (n = 107)
SIP (n = 103)

than one feature set. Multiview biclustering has been used to simultaneously cluster symptoms and brain features in adults with a range of psychopathology (114–116). There are currently no studies applying multiview biclustering to samples of youths, suggesting a promising area for future work.

A method conceptually related to multiview biclustering is similarity network fusion. Similarity network fusion is a multiview approach that creates networks of individuals based on each feature set separately and then integrates these into a single network (117). Similarity network fusion has identified clusters of youths with schizophrenia spectrum disorder, autism spectrum disorder, or bipolar disorder using demographics, brain imaging, and behavioral data (118). Methods that consider multiple feature sets will likely better represent the complex interactions that exist between clinical symptoms and biological data; as such, this approach may have great relevance to studies of brain development in youths.

METHODOLOGICAL CONSIDERATIONS IN STUDIES OF HETEROGENEITY

Data and Subject Inclusion

Single-view and multiview approaches share several issues in common across both dimensional and categorical methods. First are the issues of which subjects and what data (imaging features or symptoms) to include. This is especially important because the results will inevitably depend heavily on the input data. For example, bifactor studies that do not measure psychosis spectrum symptoms will not find a thought disorder factor. Any variance associated with psychosis spectrum symptoms may be aliased into the remaining factors, possibly impacting the dimensions or clusters discovered. Likewise, many clustering methods require defining a patient group for clustering; thus, how the sample is defined (e.g., transdiagnostic or a particular disorder only) will have a large impact on the clusters found. Specific to clustering, there is also debate as to whether healthy participants should be clustered separately or in combination with patients (19,79). Despite evidence of neurobiological heterogeneity within healthy control subjects (79,110,111,119), they are often treated as a homogeneous group (120). Taken together, it is important to carefully consider which individuals and measures will be included for all methods discussed.

Choice of Approach

A second common issue across approaches is the existence of multiple ways to parse heterogeneity in clinical groups depending on the approach chosen (19). While this was noted by Marquand *et al.* (19) in regard to clustering methods, this issue also applies to dimensional approaches. There are many supervised, semisupervised, and unsupervised algorithms for clustering, and while beyond the scope of this review, each has its own strengths and limitations (121). Different algorithms may suggest different clustering solutions, and there is currently no strong consensus on the best method for choosing the optimal number of clusters (19). Similarly, there is considerable debate regarding the appropriate method to delineate psychopathology factors using dimensional approaches. These methods differ to the degree to which they are theory-driven (confirmatory) or data-driven (exploratory), which will impact the interpretation of the resulting factors. A comprehensive review of these issues as they relate to the bifactor model is provided elsewhere in this special issue. As Feczko *et al.* (119) point out, the goal or question at hand should drive methodological choices, as different approaches may be valid for different purposes (e.g., differentiating subtypes of patients, investigating symptom latent structure, predicting treatment response).

Consideration of Covariates

Also related to the approach used is the issue of whether or not to control for covariates. This is not commonly discussed in single-view dimensional approaches such as factor analyses of symptom data, and it remains an open question as to whether it is necessary or even desirable to consider covariates in approaches that examine only symptoms. However, controlling for covariates in multiview approaches that include both symptoms and neurobiological measures is important, as there are known confounds associated with neuroimaging measures. In cross-sectional data spanning a large age range in youths, both age and sex are commonly controlled for (see Considerations for Future Research for a discussion of the need for longitudinal designs), as well as motion or data quality. Controlling for covariates may be especially important for methods that cluster based on neurobiological measures, as clustering algorithms may inadvertently produce clusters based on irrelevant variables with known relationships with brain features (e.g., clusters separated by younger and older age or by female and male sex). For many approaches, covariates can simply be regressed out of the features of interest before clustering or subject-level weighting can be used to address confounds (122). Additionally, multiview factor analytic approaches that consider covariates have been developed (123).

Figure 2. General psychopathology is associated with common neurobiological deficits in youths. Single-view dimensional approaches that identify a general factor common across disorders in youths reveal **(A)** globally reduced gray matter (GM) volume (22); **(B)** bilateral gray matter volume reductions in regions chosen a priori, including dorsal prefrontal cortex (DPFC), ventrolateral prefrontal cortex (VLPFC), and orbitofrontal cortex (OFC) (43); **(C)** reduced activation in regions within the cingulo-opercular control network during an *n*-back working memory task (44); **(D)** reduced fractional anisotropy (FA) in the genu and body of the corpus callosum (46); **(E)** elevated cerebral blood flow (CBF) in the dorsal and rostral anterior cingulate (45); and **(F)** delay in connectome distinctiveness compared with healthy control subjects across the whole brain (47). ACC, anterior cingulate cortex; ADD, attention deficit disorder; DEP, depression; gf, general factor; GPF, general psychopathology factor; L, left; R, right; SIP, structured interview for prodromal symptoms. (All figures reprinted with permission [Kaufmann *et al*. (47) copyright © 2017, *Nature Neuroscience*, Springer Nature; Reim *et al*. (46) copyright © 2019, *Behavioural Brain Research*, Elsevier; Snyder *et al*. (43) copyright © 2017, *Clinical Psychological Science*, SAGE Publications; Shanmugan *et al*. (44) and Kaczkurkin *et al*. (22) copyright © 2016 and © 2019, *American Journal of Psychiatry*, American Psychiatric Association. All rights reserved].)

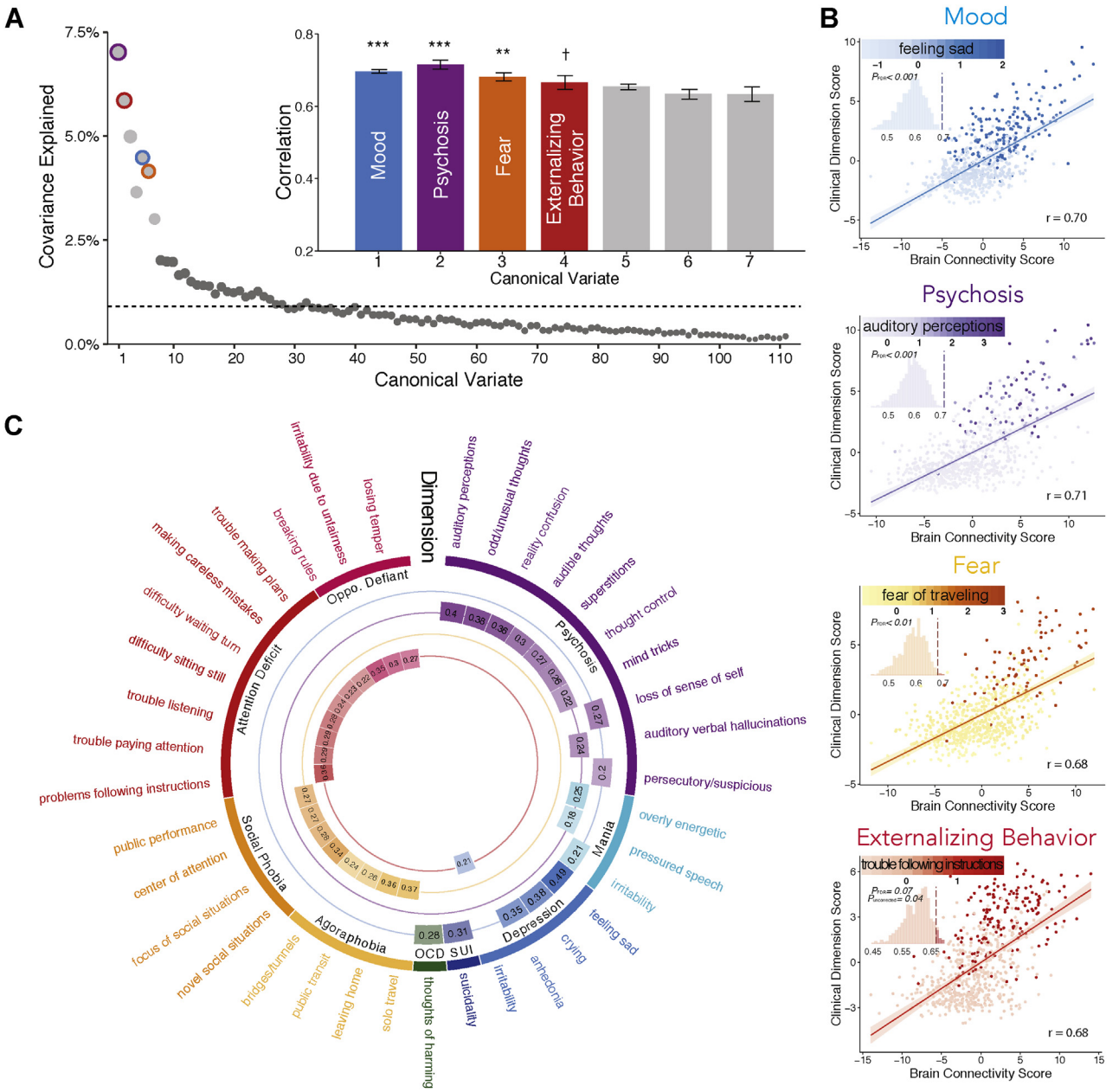


Figure 3. Sparse canonical correlation analysis links dimensions of psychopathology to functional connectivity patterns in youths. **(A)** Sparse canonical correlation analysis reveals 3 symptom dimensions (mood, psychosis, and fear) that were statistically significant, with the fourth dimension (externalizing behavior) showing an effect at uncorrected thresholds. **(B)** Scatter plots showing linear combinations of functional connectivity and psychiatric symptoms demonstrate the correlated multivariate patterns of connectomic and clinical features. **(C)** Connectivity-informed dimensions of psychopathology cross clinical diagnostic categories. Specifically, the mood dimension was composed of a mixture of depressive symptoms, suicidality, irritability, and recurrent thoughts of self-harm. The psychotic dimension was composed of psychosis-spectrum symptoms as well as 2 manic symptoms. The fear dimension comprised social phobia and agoraphobia symptoms. The externalizing behavior dimension showed a mixture of symptoms from attention-deficit/hyperactivity and oppositional defiant disorders as well as irritability from the depression section (72). OCD, obsessive-compulsive disorder; Opp., oppositional; SUI, suicidality. [Reprinted with permission (http://creativecommons.org/licenses/by/4.0/).]

Issues Regarding Sample Size

An additional consideration that applies to all approaches is the issue of adequate sample size. The methods reviewed typically require very large sample sizes to increase the stability of the results. Some methods are constrained by sample size. For example, factor analytic approaches and CCA are limited by the ratio of observations (subjects) to model features (variables), with more observations than variables

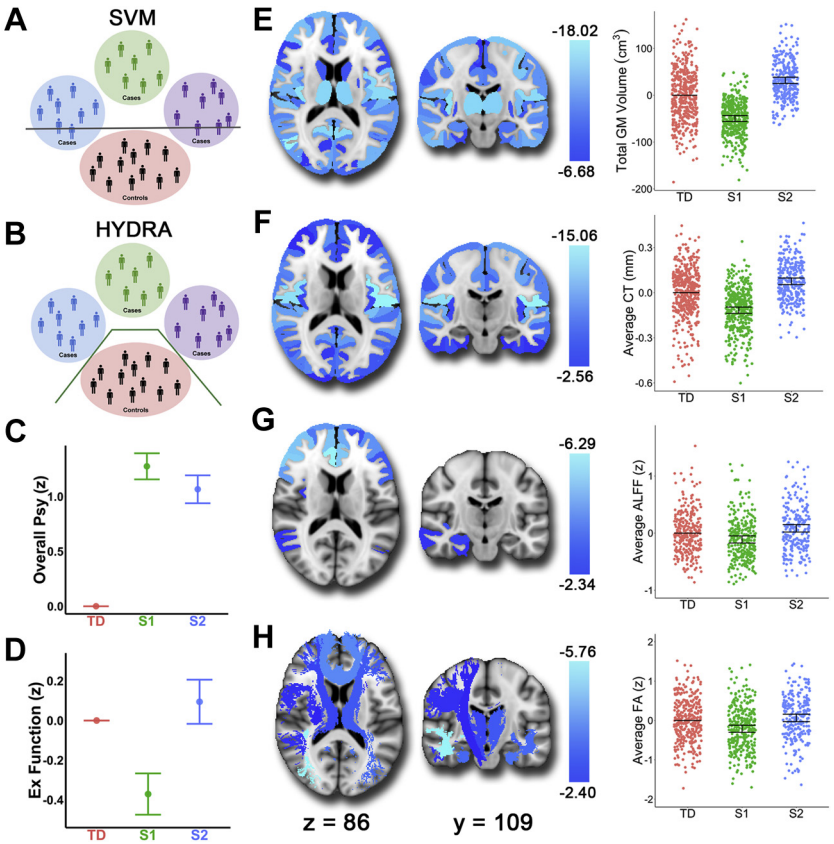


Figure 4. HYDRA identifies 2 neurostructural subtypes of internalizing youths. **(A)** A linear support vector machine (SVM) is a discriminative classifier defined by a separating hyperplane, shown here as a gray line. Linear SVMs fail to capture the heterogeneity that exists in the patients, indicated by blue, green, and purple subtypes within the cases. **(B)** Conversely, methods such as HYDRA (94) can estimate multiple linear hyperplanes (green lines) whose segments separate the clusters of cases from the controls. This approach makes HYDRA more flexible than SVMs, facilitating the identification of heterogeneous subtypes of patients. **(C)** HYDRA identified 2 subtypes of internalizing youths with a high degree of reliability. Subtype 1 (S1) and subtype 2 (S2) youths both showed significant psychopathology compared with typically developing (TD) youths. **(D)** S1 youths showed significantly worse performance than the other 2 groups on cognitive measures, especially executive functioning tasks. **(E)** In terms of structural measures, S1 youths showed smaller volumes than the other 2 groups consistently across the brain. **(F)** S1 youths also showed reduced cortical thickness in most regions. **(G)** S1 youths demonstrated reduced resting-state amplitude of low-frequency fluctuations (ALFF) in frontal regions, the right amygdala, and the right hippocampus. **(H)** Finally, S1 youths showed reduced fractional anisotropy (FA) in a number of white matter tracts. Taken together, this study showed that clustering approaches can be used to identify reliable subtypes of internalizing youths, with S1 showing greater deficits across symptoms, cognition, and brain structure (112). CT, cortical thickness; Ex, executive; GM, gray matter; Psy, psychopathology.

required (51). While clustering methods and multiview techniques such as PLS may produce results in smaller samples that have many features, the results may have poor stability, generalizability, or both. Cross-validation and replication in independent samples can increase our confidence in the results but may require even greater sample sizes and access to independently collected datasets with comparable measures. Leveraging large, publicly available neuroimaging studies will be especially helpful moving forward. Available resources include the Nathan Kline Institute–Rockland Sample (124); the Philadelphia Neurodevelopmental Cohort (125); the Pediatric, Imaging, Neurocognition, and Genetics study (126); the Human Connectome Project-Lifespan studies (127); the Healthy Brain Network (128); and the ABCD (Adolescent Brain Cognitive Development) study (129).

Interpretation Issues

There are a number of interpretation issues to take into consideration for the methods discussed. For single-view dimensional approaches such as factor analysis, methodological choices for addressing correlations between factors will impact the interpretation of the results. For example, while correlated traits models allow resultant factors to be highly correlated with one another resulting in a high degree of overlap between these factors (39), bifactor models produce orthogonal (uncorrelated) factors (39). The symptom factors in a bifactor model represent the specific variance not accounted for by general psychopathology (e.g., the fear factor represents the unique fear symptoms not shared across disorders). Thus, the presence or lack of orthogonality needs to be taken into consideration when interpreting these symptom factors. Likewise, interpretability is also an important issue in categorical approaches. The progress in developing and implementing different clustering algorithms has outpaced the research on evaluating the validity of the results (130). Notably, some clusters may be so small as to no longer be meaningful, and some individuals may not fit into any cluster (19). Finally, for both dimensional and categorical approaches, it is also unclear whether data reduction for high-dimensional data will help or hinder interpretability. Data reduction is widely used, but few studies address its impact on the results. Validation on an independent dataset or feature type will be useful for evaluating whether the results are biologically meaningful.

Reproducibility and Generalizability

Finally, it is important to consider the reproducibility and generalizability of results in studies that attempt to parse heterogeneity. While there are varying opinions in the field as to the definition of reproducibility as opposed to replicability (131), here we take Plesser's recommendation to adapt Goodman's definitions of 1) methods reproducibility, providing

sufficient detail about procedures and data so that the same procedures could be exactly repeated; 2) results reproducibility, obtaining the same results from an independent study with procedures as closely matched to the original study as possible; and 3) inferential reproducibility, drawing the same interpretive conclusions (132). Both results reproducibility and inferential reproducibility are related to the generalizability of the results. Importantly, the stability of subgroups derived from clustering methods over time has been brought into question (19), and generalizability to new samples remains challenging for all methods discussed (133). Reproducibility and generalizability may be improved when out-of-sample validation methods are employed using best practices (119,134). While the reproducibility crisis in the field is not exclusive to the methods covered in this review (135), the high-dimensional, multivariate nature of the data in conjunction with relatively small sample sizes inevitably impacts reproducibility. Thus, it will be important for researchers to provide transparent documentation of the decisions made at each step and to validate their results using appropriate methods.

CONSIDERATIONS FOR FUTURE RESEARCH

Importance of Considering Brain Maturation in Youths

As should be apparent from this review, only a limited number of studies have applied these approaches to samples of youths, suggesting a potential area growth for the field. Additionally, the studies reviewed have relied primarily on cross-sectional data spanning wide age ranges, which has clear limitations for studying development. Currently, most cross-sectional studies simply control for age effects, either by including age as a covariate in the model or by removing age effects before clustering. Treating age as a confound—rather than the primary effect of interest—is not ideal for approaching primary developmental questions of interest. Longitudinal designs have long been considered the gold standard in developmental research (136), and the dynamic nature of longitudinal trajectories of brain development is well illustrated elsewhere in this special issue. Thus, it will be important for future work to apply the approaches reviewed to longitudinal samples to determine whether neurobiological patterns change throughout development. Future work that capitalizes on large, longitudinal studies such as the ABCD study (129) will be extremely useful in this regard.

Considering Circularity in Data-Driven Approaches

One of the primary goals of data-driven approaches that aim to reconceptualize psychopathology is to provide an alternative to clinically defined DSM categorical diagnoses. However, many of the methods reviewed still rely to varying degrees on DSM-defined symptoms, introducing potential circularity into the data-driven discovery of brain-behavior relationships. For example, the clinical symptoms used in a bifactor analysis or CCA often come from clinical interviews or self-report measures based on symptoms established by DSM. Likewise, many clustering methods require defining a patient group to cluster on beforehand, which is typically defined using DSM criteria. If our input symptom measures or patient groups are heavily influenced by DSM-defined diagnoses, then it is possible that our output may broadly align with these DSM categories. Such circularity may conflict with the goal of identifying underlying heterogeneity to redefine traditional diagnostic categories. Importantly, it is possible that the symptoms defined by DSM through years of observation and scientific study could be the most relevant for data-driven exploration. Future work may be able to mitigate this circularity to some degree by applying these methods to representative samples that 1) do not exclude comorbidity, 2) include symptoms spanning the continuum from health to disorder, 3) assess the full range of psychiatric symptoms, and 4) include atypical or less common symptoms. Additionally, alternatives to using DSM-defined constructs should be explored, including studies framed around longitudinal functional outcomes (137) and treatment response across disorders (60).

Utility of Modeling Symptoms and Neurobiology Simultaneously

Studies that employ data-driven approaches to drive discovery of neural circuits associated with psychopathology represent a potential advance over the traditional case-control approach that dominated the field for years. The approaches discussed have propelled research beyond simple group differences to consider common circuit-level deficits that drive comorbidity and heterogeneous biological mechanisms within clinical syndromes. Methods that take into account more than one feature set at the same time may be particularly valuable. While single-view approaches that consider a single set of features remain useful for specific goals (e.g., redefining the classification of psychopathology symptoms), modeling more complex relationships between symptoms and biological measures will necessitate the development and further refinement of methods that can consider multiple features sets simultaneously. Moving forward, it will be important to assess for convergence using multimodal data, including clinical symptoms, neuroimaging features, neuropsychological measures, genetics, and cellular and molecular measures. Thus, future work would benefit from the application of advanced methods such as multikernel learning, generalized CCA, and multiview biclustering to integrate these increasing numbers of data types.

CONCLUSIONS

Taken together, the approaches reviewed here can be useful for redefining our understanding of heterogeneity in psychopathology. A reconceptualization of psychiatric disorders using these data-driven methods may move the field forward beyond traditional symptom-defined categories. Critically, additional research is needed using these methods in younger samples with longitudinal designs. Parsing heterogeneity in youth is a critical first step toward advancing interventions that target the pathophysiological mechanisms underlying psychopathology.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the National Institute of Mental Health (Grant No. K99MH117274 [to ANK], Grant Nos. R01MH107703, R01MH113550, and R01MH120482 [to TDS], Grant No. R01NS085211 [to RTS], and Grant No. R01MH112847 [to RTS and TDS]), Lifespan Brain Institute at the Children's Hospital of Philadelphia and Penn Medicine, and National Alliance for Research on Schizophrenia and Depression Young Investigator Award (to ANK).

RTS has received legal consulting and advisory board income from Genentech/Roche. The other authors report no biomedical financial interests or potential conflicts of interest.

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Received Jul 8, 2019; revised Nov 7, 2019; accepted Dec 11, 2019.

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