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The Hierarchical Taxonomy of Psychopathology and the Search for Neurobiological Substrates of Mental Illness: A Systematic Review and Roadmap for Future Research

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Understanding the neurobiological mechanisms involved in psychopathology has been hindered by the limitations of categorical nosologies. The Hierarchical Taxonomy of Psychopathology (HiTOP) is an alternative dimensional system for characterizing psychopathology, derived from quantitative studies of covariation among diagnoses and symptoms. HiTOP provides more promising targets for clinical neuroscience than traditional psychiatric diagnoses and can facilitate cumulative integration of existing research. We systematically reviewed 164 human neuroimaging studies with sample sizes of 194 or greater that have investigated dimensions of psychopathology classified within HiTOP. Replicated results were identified for constructs at five different levels of the hierarchy, including the overarching p-factor, the externalizing superspectrum, the thought disorder and internalizing spectra, the distress subfactor, and the depression symptom dimension. Our review highlights the potential of dimensional clinical neuroscience research and the usefulness of HiTOP while also suggesting limitations of existing work in this relatively young field. We discuss how HiTOP can be integrated synergistically with neuroscience-oriented, transdiagnostic frameworks developed by the National Institutes of Health, including the Research Domain Criteria, Addictions Neuroclinical Assessment, and the National Institute on Drug Abuse's Phenotyping Assessment Battery, and how researchers can use HiTOP to accelerate clinical neuroscience research in humans and other species.

General Scientific Summary

Clinical scientists have discovered that mental disorders are not discrete categorical entities, as assumed by traditional diagnostic models, but rather reflect variation on a number of symptom dimensions varying continuously in the general population. In response, clinical neuroscience research has increasingly studied associations of neural variables with dimensional assessments of psychopathology, which can be organized by the Hierarchical Taxonomy of Psychopathology (HiTOP). Using HiTOP as our framework, we review findings from 164 neuroimaging studies with reasonably large samples, highlighting replicated results, and we provide suggestions and guidelines for future HiTOP-informed neuroscience research.

Keywords: Hierarchical Taxonomy of Psychopathology, clinical neuroscience, Research Domain Criteria, Addictions Neuroclinical Assessment, National Institute on Drug Abuse's Phenotyping Assessment Battery

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Neuroscientific approaches are likely to be important for understanding the etiology of mental illness and for guiding the development of more effective assessments and interventions. Despite massive funding, however, progress in identifying robust neural correlates of psychopathology, to say nothing of biomarkers that might be used in diagnosis, has been very slow. This lack of progress in part reflects a heavy reliance on underpowered samples (Button et al., 2013; Marek et al., 2022), but merely collecting larger samples will not, by itself, solve the problem. A growing scientific consensus is that another key impediment is reliance on traditional categorical diagnostic systems, which group heterogeneous patients together and assume that mental disorders are discrete categorical entities (Caspi et al., 2020; Insel et al., 2010; Kotov et al., 2021; Latzman et al., 2020; Redish & Gordon, 2016).

Dimensional approaches to classifying and measuring psychopathology provide an alternative that avoids the most important limitations of categorical nosologies. The corpus of dimensional clinical neuroscience research has grown rapidly, rendering it increasingly difficult to synthesize new findings for cumulative science. This synthesis may be aided by the Hierarchical Taxonomy of Psychopathology (HiTOP), a quantitatively derived, dimensional nosology developed by a grassroots consortium of clinicians and scientists (Kotov et al., 2017, 2021). Here, we systematically review 164 studies in human clinical neuroscience that are consistent with the HiTOP approach, highlighting replicated findings. Our results suggest how HiTOP can contribute to future research, complementing several U.S. federal initiatives focused on dimensional constructs, such as the Research Domain Criteria (RDoC; Insel et al., 2010).

HiTOP Versus Traditional Psychiatric Nosologies

Official classification systems for mental illness, such as the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2013) and the *International Classification of Diseases* (World Health Organization, 2018), are rooted in a diagnostic paradigm of categorical disease entities, each with its own set of symptoms, which indicate the presence of that particular illness when sufficient in number and duration. (Throughout, we use "symptoms" broadly to include observable signs as well as subjective experience.) Extensive research on comorbidity and the distributions and covariation of symptoms has revealed that this categorical diagnostic paradigm fails to reflect the reality of mental illness. Indeed, the distribution of psychopathology is dimensional rather than categorical; no common mental disorder has ever been empirically verified as a categorical entity (Haslam et al., 2020), and it is well established that binary diagnostic categories reduce reliability and validity (and often statistical power) relative to corresponding dimensional assessments of symptom severity (Kotov et al., 2021; Markon et al., 2011; Tiego et al., 2023).

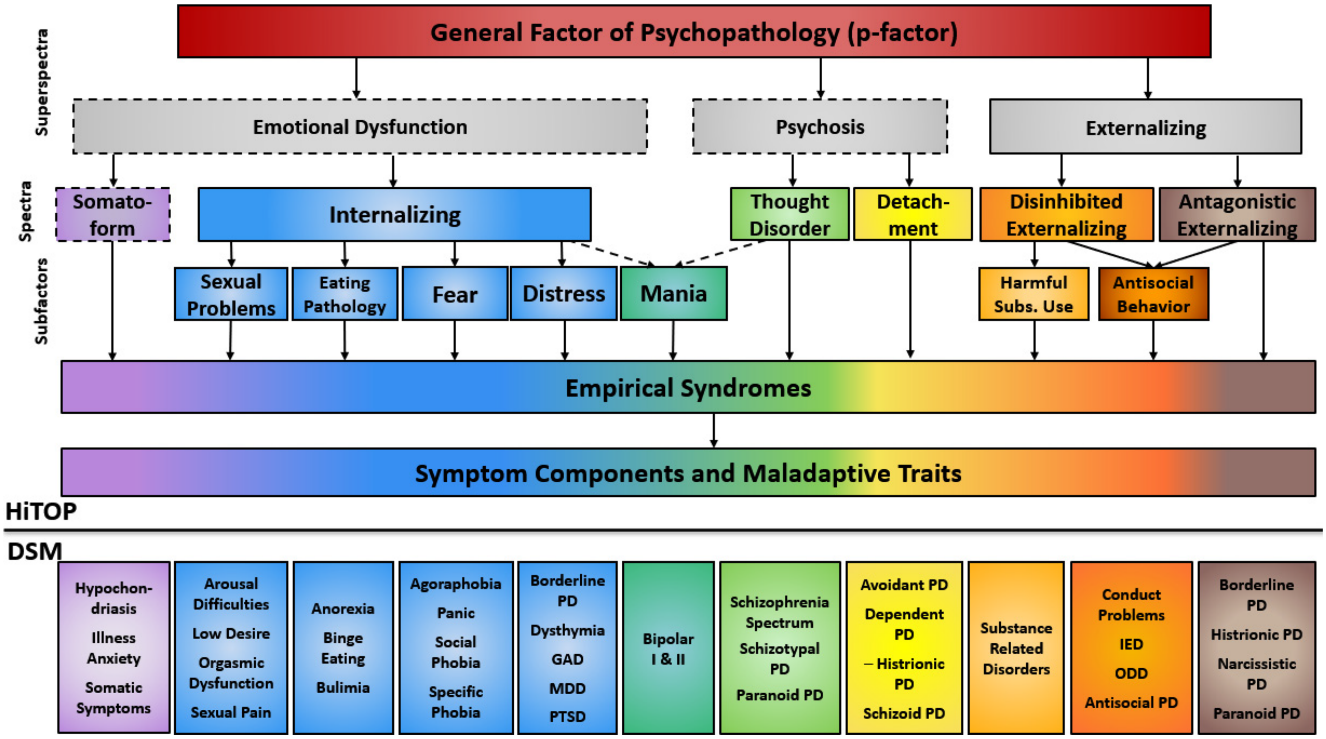
In addition to relying on symptom cutoffs that typically lack empirical justification, current categorical diagnoses also tend to include heterogeneous sets of symptoms, such that patients with the same diagnosis can have very different or even nonoverlapping symptom profiles. Furthermore, symptoms often overlap extensively between diagnoses, contributing to high rates of comorbidity (Caspi et al., 2020; Forbes, Neo, et al., 2024; Kessler et al., 2005). Quantitatively derived, dimensional models of

psychopathology offer a promising means to address these limitations, but shifting to a dimensional nosology requires a consensus model that serves research and can also be implemented effectively in clinical settings.

Based on the corpus of quantitative psychopathology research from the last several decades, HiTOP provides a hierarchical, dimensional system that is being developed to encompass the full range of psychiatric clinical conditions (Figure 1, and see https://www.hitop-system.org). (Although HiTOP is not yet fully comprehensive—for example, not yet encompassing symptoms of autism or assessments based on cognitive tests—development of the system to include all clinical phenomena is ongoing; Forbes, Ringwald, et al., 2024.) The most important feature of HiTOP is that the structure of its dimensions and levels is quantitatively derived from empirical data on covariation among symptoms and diagnoses (Kotov et al., 2017, 2021, 2022; Ringwald et al., 2021). The validity of HiTOP has been demonstrated extensively in previous publications (Kotov et al., 2017, 2020, 2021; Krueger et al., 2021; Watson et al., 2022), and it can already be employed effectively in clinical settings (Kotov et al., 2022; Ruggero et al., 2019).

By arranging clinical phenotypes into transdiagnostic spectra and superspectra, HiTOP accommodates the pervasive comorbidity and low treatment specificity that plague categorical diagnoses while minimizing heterogeneity by delineating empirically coherent dimensions. HiTOP does not assign people to a single dimension. Rather, every individual is characterized by their profile of scores across all dimensions and may have elevated scores on multiple dimensions. Individuals are characterized simultaneously using the broad spectra and superspectra dimensions and using the narrower dimensions below. Thus, HiTOP's hierarchical structure enables both lumping and splitting approaches to psychopathology. For example, if someone has a problem involving fear (e.g., phobia), Figure 1 illustrates how HiTOP lumps fear together with other forms of internalizing, thus recognizing important commonalities among all internalizing problems, which may benefit from similar treatment (Barlow et al., 2017). However, it also splits the fear subfactor from the three other subfactors of internalizing (distress, eating pathology, and sexual problems) to indicate that they are importantly distinct and are likely to have partially distinct etiologies and effective treatments. In other words, any given problem on a lower level dimension may benefit

Figure 1
The HiTOP



Note. Recent efforts by an international consortium of researchers have produced this dimensional system for organizing psychiatric symptoms (Kotov et al., 2017, 2020, 2021, 2022; Krueger et al., 2021; Ringwald et al., 2021; Watson et al., 2022). Figure depicts a simplified version of the HiTOP working model (top) and its approximate correspondence to *DSM* constructs (bottom). Constructs toward the top of HiTOP are broader and more general, whereas those at lower levels are narrower and more specific. For specific constructs at the lower HiTOP levels, see Kotov et al. (2017, 2022). HiTOP is a work in progress and will be updated on the basis of new data. Dashed lines indicate provisional elements requiring more study. Categorical diagnoses from *DSM* are not HiTOP constructs but are included to allow mapping of existing nosologies onto HiTOP, and those with the most prominent cross-loadings are listed in multiple places. Minus sign indicates negative association between histrionic personality and the detachment spectrum. HiTOP = Hierarchical Taxonomy of Psychopathology; *DSM* = *Diagnostic and Statistical Manual of Mental Disorders*; Subs. = substance; PD = personality disorder; GAD = generalized anxiety disorder; MDD = major depressive disorder; PTSD = posttraumatic stress disorder; IED = intermittent explosive disorder; ODD = oppositional defiant disorder. See the online article for the color version of this figure.

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from multiple interventions, some of which are also effective for other problems in the same spectrum or superspectrum and some of which are specifically effective for that problem.

HiTOP facilitates the investigation of neurobiological mechanisms at multiple levels of the hierarchy. Neurobiological variables can be associated either with a broad range of symptoms (correlates of upper level constructs) or with a narrow range of symptoms (correlates of lower level constructs). HiTOP thus enables the discovery and comparison of transdiagnostic neurobiological systems at different levels of breadth, a possibility not readily afforded by research designed around categorical diagnoses (Conway et al., 2019; Zald & Lahey, 2017). In short, HiTOP dimensions provide targets that should be more useful for clinical neuroscience than binary diagnostic categories comprising heterogeneous symptoms.

Some of the best evidence for this assertion comes from studies that compare effect sizes for dimensional assessments and binary diagnoses. Because there is so much variation in methods in neuroimaging research, even for very similar research questions, comparing effect sizes from different studies is often uninformative. Further, many neuroimaging studies do not report effect sizes at all, relying on brain maps of significance to convey their findings, and often there is no easy way to compute effect sizes from what is reported. Thus, the crucial studies for comparing effect sizes for different measures of psychopathology are head-to-head comparisons in the same sample. At least three such studies have found that neural variables are more strongly associated with dimensions of psychopathology than with diagnoses when both are assessed in the same samples (Kircanski et al., 2018; Martin et al., 2021; Reininghaus et al., 2019).

Neural Correlates of HiTOP Dimensions

Many neuroimaging studies have reported associations of brain structure and function with dimensions of psychopathology relevant to HiTOP. HiTOP provides a framework in which to locate dimensional psychopathology constructs, and existing assessments can be classified within HiTOP if they use psychometrically sound measures of dimensions represented in HiTOP or if they are latent variables that model those dimensions as shared variance across multiple symptoms or diagnoses. Taking advantage of this integrative potential for HiTOP, we conducted a systematic, qualitative review of reasonably large studies in various neuroimaging modalities (e.g., magnetic resonance imaging [MRI], electroencephalography [EEG]), spanning multiple levels of the HiTOP model. The goal of this review was to summarize the current state of the relatively young field of dimensional approaches to clinical neuroimaging, identifying the scope of research already conducted in this area, assessing the degree to which studies have converged on replicated findings, and providing a list of individual findings that might warrant replication attempts. This review was not intended to answer a specific empirical question or to provide an assessment of effect sizes. It was not preregistered, and we did not adopt every guideline from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses system, but our goal was to provide a thorough and unbiased overview of the field.

Our procedure for conducting the review is summarized here, and full details may be found in our online supplemental material. We searched PubMed for the conjunction of three lists of terms: (a) terms describing neuroimaging methods; (b) terms referring broadly to mental illness, psychopathology, and psychiatry; and (c) specific constructs, frameworks, and statistical approaches of interest. Subsequently, we canvased members of the HiTOP Neurobiological Foundations workgroup to identify missing studies. Criteria for study eligibility included the use of dimensional assessments or latent variable models of psychopathology, as well as a minimum sample size of 194 participants, the number necessary for 80% power to detect a product–moment correlation of .20 at $p < .05$. This effect size was chosen because it is approximately the median reported effect size in meta-analyses of psychological research on individual differences and is conventionally considered small to moderate (Gignac & Szodorai, 2016; Hemphill, 2003). Smaller samples are unable to estimate such effects accurately, due to sampling variability (Schönbrodt & Perugini, 2013), and one unfortunate consequence of this lack of precision is that a larger proportion of significant findings are false positives when studies are underpowered. This problem is further exacerbated when many statistical tests are conducted, as in many neuroimaging studies.

Recent research on individual differences in neuroimaging data indicates that univariate associations of symptom dimensions with neural correlates in structural MRI and resting state functional connectivity data are typically likely to be even smaller than $r = .20$ (Marek et al., 2022). This finding suggests a cutoff even larger than 194, but we felt it was important to capture a reasonably comprehensive cross-section of existing research. Thus, our sample-size criterion is a compromise between maintaining adequate statistical power for trustworthy results and acknowledging the general tendency of the field to conduct underpowered studies.

We required that samples were from either the general population (whether or not the sample was enriched for one or more diagnoses or for high scores on some dimension of psychopathology) or a mixed-diagnosis population containing patients selected on at least two diagnoses falling in at least two different HiTOP spectra (to reduce problems related to restriction of range in single-diagnosis samples). Case–control designs were excluded.

After 4,735 initial hits, 151 studies were retained following exclusions based on sample, assessment, and analytic criteria, and 13 other studies meeting our criteria were added after being identified by HiTOP members (Figure 2). Characteristics and results for all 164 studies are tabulated in the online supplemental materials. Retained studies covered all six HiTOP spectra, some at the spectrum level and some assessing lower level constructs within those spectra (Figure 3). Additionally, 35 studies focused on the p-factor (which represents the shared variance among all more specific forms of psychopathology), either by itself or in conjunction with lower level constructs. Regarding methods, 128 studies used one or more forms of MRI. The most frequent MRI modalities were structural MRI (57 studies), resting-state functional connectivity (51 studies), task-based functional MRI (25 studies), and diffusion-weighted imaging of white matter (22 studies). Thirty-five studies used EEG data.

Given the broad scope of our review, we focus our discussion on replicated results (Table 1), here defined as those that were significant, in the same direction, for the same HiTOP construct, in two or more independent samples, using the same neuroimaging modality with similar methods (thus, for example, a task-based fMRI result would not be considered to replicate a resting-state fMRI result, even if they implicated the same brain region). HiTOP constructs could be measured by different assessment methods as long as they were identifiable as the same construct. Our goal with this relatively permissive set of criteria for replication was not to determine whether replicated findings were robust or to provide effect-size estimates.

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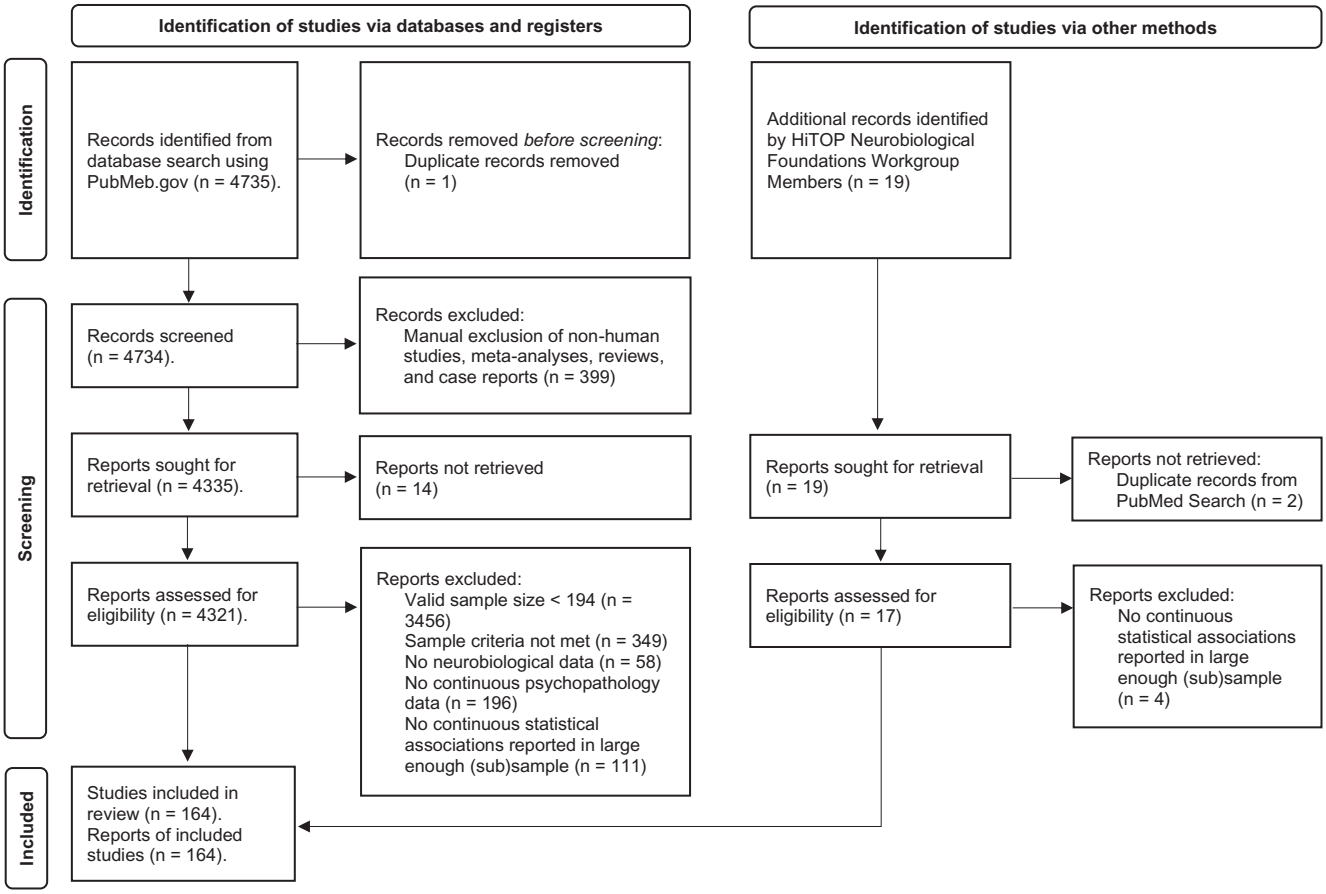
Figure 2

Flow Chart of Study Selection Process for Review



Note. HiTOP = Hierarchical Taxonomy of Psychopathology.

Instead, our summary of replicated results is intended to highlight some findings that may be especially worth following up in future research. We also note when any additional studies failed to replicate the replicated results using similar methods. The summary is organized in terms of superspectra and spectra, with narrower dimensions discussed with the relevant spectrum.

P-Factor Superspectrum

Replicated structural findings for the p-factor indicate that it is negatively associated with various MRI measures of global brain size, including intracranial volume but also gray matter volume, mean cortical thickness, and cortical surface area (Durham et al., 2021; Kaczkurkin et al., 2019; Lees et al., 2020; Roalf et al., 2017; Romer et al., 2021). We group these results together because gray matter volume is a substantial component of intracranial volume and a function of cortical thickness and surface area. These results are consistent with a recent genome-wide association study of shared risk across diagnoses, which pinpointed four common genetic variants believed to play a role in fetal cortical development (Schork et al., 2019). One possibility is that underdeveloped cortical size is associated with a general risk for psychopathology because it reflects some very general properties of brain function. Another possibility is that smaller size in some specific large-scale brain networks (a likely consequence of reduced overall cortical size) is associated with poorer function that creates broad risk. The latter possibility is consistent with two other replicated findings: first, the p-factor is associated with reduced functional segregation of the control or executive network from other major brain networks, as indicated by greater synchrony of this network with other networks (Chen et al., 2022; Elliott et al., 2018; Lees et al., 2021; Sripada et al., 2021; Xia et al., 2018); and, second, the p-factor is associated with reduced functional connectivity within a network often labeled the "default network" (Chen et al., 2022; Karcher et al., 2021; Sripada et al., 2021), which is involved in memory, prospection, imagination, self-evaluation, and perspective taking (Andrews-Hanna et al., 2014). (Note that the default network finding counts as replicated, by our criteria, because one study split the Adolescent Brain and Cognitive Development sample in half and found the effect independently in each subsample of $n > 3{,}700$.)

Externalizing Superspectrum

The externalizing superspectrum encompasses the shared variance of antagonistic externalizing (aggression, callousness, deceitfulness, etc.) and disinhibited externalizing (impulsivity, distractibility, drug

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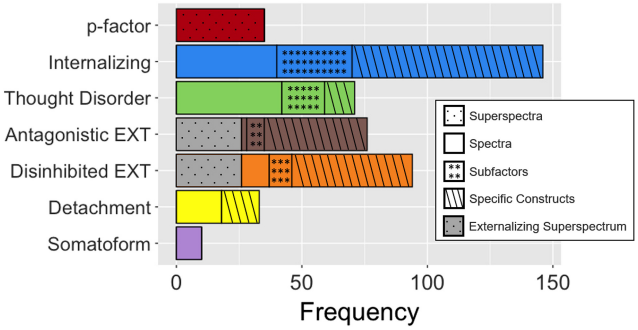
Figure 3

Frequency of Studies in Review Investigating Different HiTOP Constructs, Separated Within Each Spectrum by Different Levels of the Hierarchy



Note. The "specific constructs" category includes constructs from the levels "empirical syndromes" and "symptom components and maladaptive traits." Studies of mania were double-counted in the subfactor category for both internalizing and thought disorder. HiTOP = Hierarchical Taxonomy of Psychopathology; EXT = externalizing. See the online article for the color version of this figure.

problems, etc.), and it has often been studied without separating its two subspectra. In seven studies, this broad externalizing factor, as well as many of its subdimensions, were associated with reduced amplitude of the P300 event-related potential in EEG, an electrophysiological index of attentional control (Bowyer et al., 2020; Costa et al., 2000; Gilmore, Malone, Bernat, et al., 2010; Gilmore, Malone, Iacono, et al., 2010; Habeych et al., 2005; Koskinen et al., 2011; Mobascher et al., 2010). (One additional study did not replicate the result; Ait Oumeziane & Foti, 2016.) This extensively replicated finding is consistent with the premise that both disinhibited and antagonistic behavior often result from a lack of top-down control, which allows disruptive impulses to be enacted in behavior (Venables et al., 2018).

Internalizing Spectrum

The internalizing spectrum was found to be positively associated with total amygdala volume in three studies (Albaugh et al., 2017; Holmes et al., 2012; Lahey et al., 2021). Although two other studies failed to replicate this association (Durham et al., 2021; Hyatt et al., 2019), it is congruent with a large body of evidence linking internalizing to the extended amygdala (Hur et al., 2019). The internalizing spectrum as a whole may reflect variation in mechanisms involved in defensive emotional and motivational responses to aversive stimuli, with its various subdimensions reflecting different aspects of that multifaceted response. Other replicated findings emerged for specific subdimensions of internalizing. Distress, a subfactor that encompasses many symptoms related to anxiety and depression, was associated negatively with volume of the rostral anterior cingulate cortex (ACC; Cohen et al., 2006; Hayakawa et al., 2014; Zhu et al., 2021). Other studies found that the narrower depression symptom dimension was negatively associated with the reward positivity, an event-related potential index of reward sensitivity. Two studies found the association with the reward positivity (Nelson & Jarcho, 2021; Nelson et al., 2016), but two others did not (Ait Oumeziane & Foti, 2016; Kessel et al., 2016). A fifth study suggests a possible reason for these inconsistencies (Goldstein et al., 2020). In a sample of children, the reward positivity was negatively associated with depression symptoms, but only for those who had experienced higher levels of stressful life events. If this finding generalizes to other populations, it would suggest that sensitivity of the reward system may be a risk factor for depression rather than a direct marker of it.

Thought Disorder Spectrum

Three replicated functional connectivity findings were identified for the thought disorder spectrum, which reflects psychotic symptoms and cognitive disorganization. First, two studies found a negative association with connectivity in the frontoparietal control network, an extensive brain network implicated in working memory and attention control (Baker et al., 2019; Blain et al., 2020). This is consistent with the general disorganization of thought and behavior seen in psychosis (Kotov et al., 2020). The second and third findings are more complicated because they seem to contradict each other. Two studies (one of which reported replication across two samples) found a positive association between thought disorder and connectivity within the default network (Blain et al., 2020; Xia et al., 2018), whereas two other studies found a negative association (Baker et al., 2019; Meda et al., 2014). Although it is possible that these contradictory results are due to differences in methodology, such as the use of different covariates and different measures of psychopathology, the most notable difference between the studies is in their samples: Those that found a positive association used general population samples, whereas those that found a negative association used samples with a large proportion of patients. Differences in the frequency of severe mental illness in the samples might lead to these very different associations between symptom severity and brain function. These conflicting results highlight an important puzzle for future research on psychosis.

Lessons and Limitations

The replicated findings cut across traditional categorical diagnostic categories. HiTOP provides a framework for investigating such cross-cutting neural correlates of psychopathology at varying levels of breadth, ranging from those that are evident across most forms of illness (p-factor), to those that are linked to more specific forms of illness (e.g., spectra), to those that are only evident for narrow symptom dimensions. One challenge for such research, evident in the studies we identified, is the great variety and often ad hoc nature of the dimensions and models employed based on measures that happen to be available in each sample. Nonetheless, we were able to map these dimensions onto HiTOP constructs, illustrating how HiTOP provides a common language for dimensional research. In the future, researchers are advised to select measures allowing thorough assessment of HiTOP dimensions, but researchers can already use HiTOP to identify which dimensions can be adequately assessed in existing data sets, thereby allowing more effective cumulative scientific progress (e.g., see list of HiTOP-conformant measures in Table 1 of Kotov et al., 2017). For instruments that have not previously been classified, we recommend searching the empirical literature for patterns of association with HiTOP dimensions or, if such evidence is not available, then careful examination of item content to determine probable correspondence. The recently released HiTOP survey instrument (https://www.3plab.org/hitop) should be useful in such content analysis.

If researchers use confirmatory or exploratory factor analysis to assess dimensions of psychopathology, then one important

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Table 1

Summary of Replicated Findings (At Least Two Consistent Findings in Independent Samples)

Finding	Citation	Sample	Clinical/diagnostic characteristics
p-factor negatively associated with ICV, GMV, total cortical surface area, or mean cortical thickness	Romer et al. (2021)	861 participants from the Dunedin study (age 45)	General population. (Used diagnostic interviews. Diagnostic status of cohort members is documented by Caspi et al., 2020.)
	Roalf et al. (2017)	1,266 participants from PNC (age 8–21, $M = 15.2$, $SD = 3.5$)	359 no diagnosis, 386 psychosis spectrum, 521 other psychopathology. (Used computerized diagnostic interviews.)
	Kaczkurkin et al. (2019)	1,394 participants from PNC (age: $M = 15.0$, $SD = 3.6$)	428 no diagnosis, 230 ADHD, 81 agoraphobia, 16 anorexia, 5 bulimia, 121 conduct disorder, 27 generalized anxiety, 193 major depression, 16 mania, 43 obsessive compulsive, 458 oppositional defiant, 14 panic, 399 psychosis spectrum, 172 posttraumatic stress, 63 separation anxiety, 328 social anxiety, 426 specific phobia. (Used computerized diagnostic interviews.)
	Lees et al. (2020)	9,719 participants from ABCD (age 9–10, $M = 9.9$, $SD = 0.6$)	264 depression, 409 generalized anxiety, 27 panic, 834 separation anxiety, 453 social anxiety, 46 hallucinations, 163 delusions, 1,870 ADHD, 1,283 oppositional defiant, 271 conduct disorder, 844 obsessive compulsive, 324 bipolar, 170 posttraumatic stress, 2,511 specific phobia. (Used diagnostic interviews.)
	Cheng et al. (2021)	11,067 participants from ABCD (age 9–11, $M = 9.9$, $SD = 0.6$)	Diagnostic characteristics not documented. (Likely consistent with other ABCD studies. Used diagnostic interviews.)
	Mewton et al. (2022)	11,875 participants from ABCD (age 9–10, $M = 9.9$, $SD = 0.6$)	318 depression, 510 generalized anxiety, 32 panic, 1,049 separation anxiety, 547 social anxiety, 55 hallucinations, 216 delusions, 2,429 ADHD, 1,667 oppositional defiant, 374 conduct disorder, 1,099 obsessive compulsive, 429 bipolar, 231 posttraumatic stress, 3,133 specific phobia. (Used diagnostic interviews.)
	Durham et al. (2021)	9,607 participants from ABCD (age 9–10, $M = 9.9$, $SD = 0.6$)	Diagnostic characteristics not documented. (Likely consistent with other ABCD studies.)
p-factor positively associated with functional connectivity between control network(s) and other networks	Elliott et al. (2018)	605 participants from the Duke Neurogenetics Study (age 18–22, $M = 20.2$, $SD = 1.2$)	472 no diagnosis, 76 alcohol use, 24 substance use, 33 depression, 26 bipolar, 7 panic, 9 agoraphobia, 4 social anxiety, 8 generalized anxiety, 10 obsessive compulsive, 7 eating disorders. (Used diagnostic interviews.)
	Xia et al. (2018)	999 participants from PNC (age 8–22, $M = 15.8$, $SD = 3.3$)	Diagnostic characteristics not documented. (Likely consistent with other PNC studies. Used computerized diagnostic interviews.)
	Sripada et al. (2021)	6,593 participants from ABCD (age 9–10, $M = 9.9$, $SD = 0.6$)	1,228 ADHD, 2,358 anxiety, 389 bipolar, 376 depression, 1,636 developmental disorder, 713 eating disorder, 658 obsessive compulsive, 906 oppositional defiant/conduct disorder, 264 posttraumatic stress, 165 psychosis, 9 substance, 609 suicidality/self-injury. (Used diagnostic interviews.)
	Lees et al. (2021)	11,721 participants from ABCD (age 9–10, $M = 9.9$, $SD = 0.6$)	5,890 no diagnosis, 2,428 ADHD, 1,666 oppositional defiant, 374 conduct disorder, 318 depression, 510 generalized anxiety, 32 panic, 1,048 separation anxiety, 547 social anxiety, 231 posttraumatic stress, 3,130 specific phobia, 55 hallucinations, 215 delusions, 1,096 obsessive compulsive, 428 bipolar. (Used diagnostic interviews.)
	Chen et al. (2022)	1,858 participants from ABCD (age: $M = 10.0$, $SD = 0.6$)	Diagnostic characteristics not documented. (Likely consistent with other ABCD studies. Used diagnostic interviews.)

(*table continues*)

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Table 1 (*continued*)

Finding	Citation	Sample	Clinical/diagnostic characteristics
p-factor negatively associated with default network functional connectivity	Sripada et al. (2021)	6,593 participants from ABCD (age 9–10, $M = 9.9$, $SD = 0.6$)	1,228 ADHD, 2,358 anxiety, 389 bipolar, 376 depression, 1,636 developmental disorder, 713 eating disorder, 658 obsessive compulsive, 906 oppositional defiant/conduct disorder, 264 posttraumatic stress, 165 psychosis, 9 substance, 609 suicidality/self-injury. (Used diagnostic interviews.)
	Chen et al. (2022)	1,858 participants from ABCD (age: $M = 10.0$, $SD = 0.6$)	Diagnostic characteristics not documented. (Likely consistent with other ABCD studies. Used diagnostic interviews.)
	Karcher et al. (2021)[a]	7,581 participants from ABCD (age 9–11, $M = 9.9$, $SD = 0.6$)	Diagnostic characteristics not documented. (Likely consistent with other ABCD studies.)
Internalizing positively associated with amygdala volume	Albaugh et al. (2017)	371 participants from the NIH MRI Study of Normal Brain Development (longitudinal data collected from age 4 to 18, mean age at scan = 12.0, $SD = 0.1$)	General population. (Those with diagnosis of simple phobia, social phobia, adjustment disorder, oppositional defiant disorder, enuresis, encopresis, or nicotine dependency were not excluded. Used diagnostic interviews.)
	Holmes et al. (2012)	1,050 participants from BGSP (age 18–35, $M = 21.4$, $SD = 3.0$)	Healthy. (Participants with self-reported psychiatric diagnoses were excluded.)
	Lahey et al. (2021)	433 participants from the Tennessee Twin Study (longitudinal questionnaire data collected in adolescence and scan in adulthood. Questionnaire $M_{age} = 13.6$, $SD = 2.5$. Scan $M_{age} = 26.0$, $SD = 1.8$)	General population. (Those with parent-reported diagnosis of autism or psychosis were excluded.)
	Durham et al. (2021)[b]	9,607 participants from ABCD (age 9–10, $M = 9.9$, $SD = 0.6$)	Diagnostic characteristics not documented. (Likely consistent with other ABCD studies.)
	Hyatt et al. (2019)[b]	1,101 participants from HCP (age: $M = 28.8$, $SD = 3.7$)	General population. (Those with a history of significant psychiatric treatment excluded.)
Distress (or constituent subfactors) negatively associated with ACC volume	Cohen et al. (2006)	265 participants from the Brain Research International Database (age 18–70, $M = 39.9$, $SD = 17.2$)	Healthy. (Screened using self-reported symptoms.)
	Hayakawa et al. (2014)	810 participants (age 23–84, $M = 55.3$, $SD = 9.8$)	Healthy. (Screening method unclear.)
	Zhu et al. (2021)	19,592 participants from U.K. Biobank (age 45–80, $M = 62.6$, $SD = 7.4$)	General population. (Including 2,103 individuals with a self-reported diagnosis of depression, schizophrenia, bipolar anxiety, posttraumatic stress, obsessive compulsive, or eating disorders.)
Depression negatively associated with reward positivity ERP	Nelson et al. (2016)	444 participants (age 13–15, $M = 14.4$, $SD = 0.6$)	General population youth. Forty first-onset depression, 113 anxiety, 21 externalizing/behavioral disorder. (Used diagnostic interviews. Those with depression at baseline were excluded.)
	Nelson and Jarcho (2021)	204 participants (age: $M = 19.9$, $SD = 2.5$)	General population (college students). Based on self-reported symptoms, 5.9% met criteria for depression and 8.4% for social phobia.
	Goldstein et al. (2020)	369 participants from the Stony Brook Temperament study (longitudinal data; baseline $M_{age} = 9.2$, $SD = 0.4$; follow-up $M_{age} = 12.7$, $SD = 0.4$)	General population. (Those with diagnosis of depression were excluded. Used diagnostic interviews.)
	Kessel et al. (2016)[b]	373 participants (longitudinal data collected at both age 3 and age 9)	General population. (Used diagnostic interviews but reported only dimensional constructs.)
	Ait Oumeziane and Foti (2016)[b]	260 participants (age: $M = 23.6$, $SD = 10.3$)	General population. (Based on DASS-21 depression, 186 were normal range, 43 mild, 21 moderate, and 7 severe.)
Thought disorder negatively associated with frontoparietal connectivity	Baker et al. (2019)	1,010 participants from BGSP (age 18–71, $M = 33.7$, $SD = 12.9$)	608 no diagnosis, 210 psychosis, 192 affective disorders. (Used diagnostic interviews.)
	Blain et al. (2020)	1,003 participants from HCP (age 22–37, $M = 28.7$, $SD = 3.7$)	General population. (Those with a history of significant psychiatric treatment excluded.)
Thought disorder positively associated with default network connectivity	Xia et al. (2018)	999 participants from PNC (age 8–22, $M = 15.8$, $SD = 3.3$)	Diagnostic characteristics not documented. (Likely consistent with other PNC studies. Used computerized diagnostic interviews.)
	Blain et al. (2020)	1,003 participants from HCP (age 22–37, $M = 28.7$, $SD = 3.7$)	General population. (Those with a history of significant psychiatric treatment excluded.)

(*table continues*)

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Table 1 (*continued*)

Finding	Citation	Sample	Clinical/diagnostic characteristics
Thought disorder negatively associated with default network connectivity	Baker et al. (2019)	1,010 participants from BGSP (age 18–71, $M = 33.7$, $SD = 12.9$)	608 no diagnosis, 210 psychosis, 192 affective disorders. (Used diagnostic interviews.)
	Meda et al. (2014)	1,305 participants from the Bipolar-Schizophrenia Network on Intermediate Phenotypes Consortium (age: $M = 37.4$, $SD = 13.8$)	324 healthy controls, 296 schizophrenia, 300 psychotic bipolar, 179 relatives of schizophrenia, 206 relatives of bipolar. (Used diagnostic interviews.)
Externalizing (or constituent subfactors) negatively associated with P300 ERP amplitude	Costa et al. (2000)	563 participants from the Collaborative Study on the Genetics of Alcoholism (age 18–49, $Mdn = 30$)	144 general population (without a history of substance dependence/misuse), 272 alcohol dependence, 26 antisocial personality, 121 comorbid alcohol dependence + antisocial personality. (Used diagnostic interviews.)
	Habeych et al. (2005)	265 participants (age 10–12, $M = 11.0$, $SD = 0.9$)	25 oppositional defiant, 10 conduct disorder, 39 ADHD, 8 depression. (Used diagnostic interviews.)
	Bowyer et al. (2020)	334 participants (age 18–47, $M = 20.7$, $SD = 4.1$)	General population (college students)—prescreened to sample low, moderate, and high externalizing.
	Mobascher et al. (2010)	1,318 participants (age 18–65, $M = 36.6$, $SD = 13.4$)	596 smokers and 722 never-smokers. (Psychiatric diagnoses were an exclusion criterion. Used diagnostic interviews.)
	Koskinen et al. (2011)	294 participants (age 23–28, $M = 25.8$, $SD = 1.0$)	185 alcohol use, three drug use, 21 antisocial personality, 107 depression, 30 anxiety, 157 current smokers. (Numbers reflect larger sample of 358, rather than the EEG sample of 294. Used diagnostic interviews.)
	Gilmore, Malone, Bernat, et al. (2010) and Gilmore, Malone, Iacono, et al. (2010)	1,938 participants from MTFS (age 17–18, $M = 18.2$, $SD = 0.7$)	24% of the sample met diagnostic criteria for at least one externalizing disorder. (Used diagnostic interviews.)
	Gilmore, Malone, Bernat, et al. (2010) and Gilmore, Malone, Iacono, et al. (2010)	506 participants from MTFS (age 17–18, $M = 17.5$, $SD = 0.4$)	71 healthy controls, 184 conduct disorder, 45 ADHD, 87 oppositional defiant, 68 nicotine use, 95 alcohol use, and 35 illicit drug use. (Used diagnostic interviews.)
	Ait Oumeziane and Foti (2016)[b]	260 participants (age: $M = 23.6$, $SD = 10.3$)	General population. (Based on DASS-21 depression, 186 were normal range, 43 mild, 21 moderate, and 7 severe.)

Note. ABCD = Adolescent Brain and Cognitive Development; ACC = anterior cingulate cortex; BGSP = Brain Genomics Superstruct Project; ERP = event-related potential; DASS = Depression Anxiety Stress Scale; HCP = Human Connectome Project; MTFS = Minnesota Twin Family Study; PNC = Philadelphia Neurodevelopmental Cohort; NIH = National Institutes of Health; MRI = magnetic resonance imaging; EEG = electroencephalography; ICV = intracranial volume; GMV = gray matter volume; ADHD = attention deficit/hyperactivity disorder.
[a] Participants in this study were split into a discovery sample ($n = 3{,}790$) and an independent replication sample ($n = 3{,}791$); finding was present in both samples. [b] Failed replication.

consideration is whether associations with neural variables are tested in latent space. Of the studies we reviewed, only 14 (9%) examined associations between psychopathology and neural variables in latent space (and seven others used canonical correlation analysis, which is analogous but not, strictly speaking, latent). Forty studies (24%) used estimated factor scores for psychopathology dimensions. Estimating factor scores moves the dimension out of latent space back to observed measurement space, and this reintroduces error variance that was removed in latent space, reducing power and accuracy and also often inflating correlations among dimensions (even if they were orthogonal in latent space). The remaining 63% of studies used observed scale scores or composites of observed scale scores. There are compelling reasons to conduct analyses of brain–behavior associations in latent space, but methodological constraints sometimes render this difficult (Tiego et al., 2023).

Another crucial issue to consider when interpreting the findings we reviewed (or when planning future research) is discriminant validity. At every level of HiTOP's hierarchy below the p-factor, there are expected correlations between dimensions (represented by their grouping within higher level dimensions). Thus, whenever researchers detect an association of some neurobiological variable with a HiTOP construct, it is important to consider (a) whether the association is unique to that construct or shared with other constructs at the same level and (b) whether the association might be due to only a subset of the dimensions nested beneath the construct in question. These questions cannot be answered unless multiple dimensions are examined, even if the study's focal hypothesis is about only one. Further, if multiple constructs at the same level are associated with the neurobiological variable of interest, then it becomes important to control for their shared variance to determine whether the effect is specific to one of them. Only 36% of the studies in our review adequately controlled for multiple dimensions of psychopathology (as indicated in the Spreadsheet in the online supplemental materials). For all those that did not, the failure to investigate discriminant validity limits the conclusions we can draw from them.

One limitation of our review is that it was not quantitative, but the diversity of research questions and methods, the relatively modest number of published studies for most constructs, and the frequent failure of neuroimaging studies to report interpretable effect sizes made meta-analysis impractical. Another limitation, which could have contributed to some of the replication failures noted above, is that the retained studies used samples of widely varying ages, including children, adolescents, and adults. Neural substrates of psychopathology may shift with age, but the relevant literature is not yet sufficiently developed to consider moderation by age in a review of this scope. The results reported here are clearly not the whole story regarding neural correlates of any HiTOP dimension. Given the complexity of the brain, each dimension of psychopathology will almost certainly be influenced by multiple neural parameters, and many other correlates therefore remain to be found. Additionally, some findings reported here could be false positives despite replication. Going forward, additional replications in adequately powered samples (ideally preregistered) are crucial, and we hope researchers find our Spreadsheet in the online supplemental materials useful for identifying other findings that are worthy of replication attempts.

Considering the dates of all included studies (see the online supplemental materials), our review shows that large studies of dimensional clinical phenotypes have recently become much more prevalent, a hopeful development for the field. At the same time, many studies have relied on a relatively small set of large samples, such as Adolescent Brain and Cognitive Development, and this is certainly a limitation that the field should attempt to overcome by collecting additional, diverse, large samples. It is notable that, for all of our replicated findings, at least some of the samples included individuals qualifying for diagnoses (see Table 1). Relatively few samples excluded individuals with some or all diagnoses, which raises confidence that findings are relevant to clinical phenomena. Additionally, almost no samples were exclusively clinical. Given that features of psychopathology are continuous dimensions, it would be unwise to limit investigations to clinical samples, which restrict the range of the variables under study. On the other hand, it is possible that some associations between psychopathology and neural variables could be nonlinear, changing in or near the clinically relevant range. Nonlinear effects have rarely been investigated, but they could be of interest in future research.

Identification of relatively broad structural and functional neural correlates, such as those covered in our review, increases knowledge about psychopathology. However, it is not yet certain how useful this approach may be in diagnosis or the development of interventions. One possibility for the future is that, as knowledge of neural correlates becomes more detailed, they could provide incremental information in diagnosis. More immediately, however, they seem likely to be useful in basic research aimed at understanding the etiology of various forms of psychopathology, such as by identifying which neural circuits to prioritize in mechanistic follow-up research in humans or other species. (One example of such synergistic research is discussed in relation to anxiety in the Connecting HiTOP to Research in Other Species section.) In the next section, we discuss using frameworks developed for neuroscientific approaches to interpret results from our review.

Integrating HiTOP With Frameworks From the National Institutes of Health (NIH)

HiTOP is not the only dimensional framework that has been proposed in response to the shortcomings of categorical diagnoses. Three NIH institutes have developed frameworks to guide research on mental disorders: RDoC, created by the National Institute of Mental Health (Insel et al., 2010; Kozak & Cuthbert, 2016); the Addictions Neuroclinical Assessment (ANA) created by the National Institute on Alcohol Abuse and Alcoholism (Kwako et al., 2016); and the National Institute on Drug Abuse's Phenotyping Assessment Battery (NIDA PhAB; Keyser-Marcus et al., 2021). These frameworks consist of dimensions grounded in neuroscience and encompass both behavioral and biological constructs.

RDoC is designed to be a flexible framework that can change over time in response to scientific developments. Currently, it lists six domains of biobehavioral systems (see Figure 4), each subsuming multiple constructs and subconstructs, to be studied across multiple units of analysis ranging from genes to neural circuits to self-reports, as outlined in the RDoC matrix (https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/constructs/rdoc-matrix.shtml). ANA includes three domains relevant to addiction—negative emotionality, incentive salience, and executive function—and NIDA PhAB includes the same three domains and adds interoception, metacognition, and sleep. RDoC, ANA, and NIDA PhAB were designed to capture specific behaviors, neural circuits, and mechanisms relevant to psychopathology. Unlike diagnostic systems, they do not aim to

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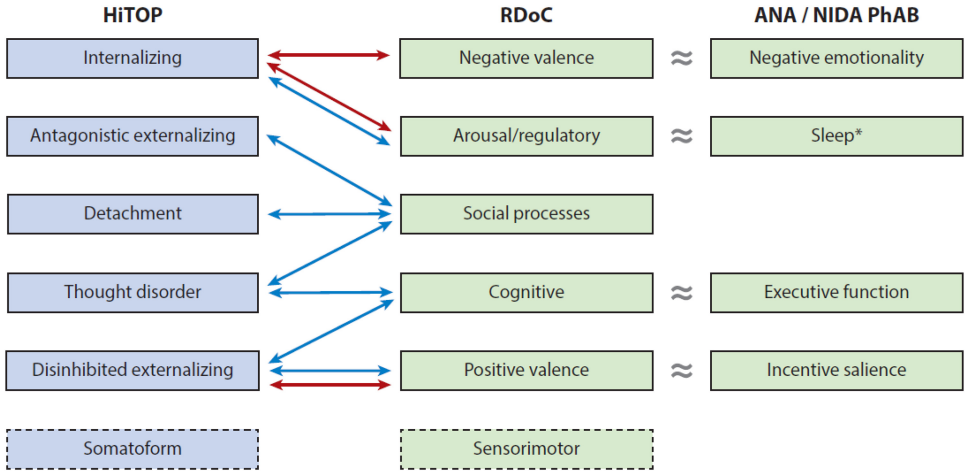
Figure 4

Initial Crosswalk Between HiTOP, RDoC, ANA, and NIDA PhAB



Note. Depicted links between HiTOP and RDoC are the strongest and most consistent associations according to a review of empirical studies (Michelini et al., 2021). Less prominent links are not shown. Due to paucity of relevant studies, it was not possible to link the recently introduced RDoC sensorimotor domain to any HiTOP spectra, nor the HiTOP somatoform spectrum to any RDoC domains. Negative associations are presented in red (darker gray) and positive associations in blue (lighter gray). Double arrows indicate that within the RDoC domain some constructs show positive links, whereas others show negative links to the HiTOP spectrum (e.g., internalizing was associated positively with arousal and negatively with sleep constructs from the arousal/regulation domain). Associations between RDoC and ANA or NIDA PhAB domains are shown with symbols for approximate equality. Asterisk indicates a domain in NIDA PhAB but not in ANA. (NIDA PhAB domains of metacognition and interoception have not been linked to RDoC and are not depicted.) HiTOP = Hierarchical Taxonomy of Psychopathology; RDoC = Research Domain Criteria; ANA = Addictions Neuroclinical Assessment; NIDA PhAB = National Institute on Drug Addiction's Phenotyping Battery. Adapted from "The Hierarchical Taxonomy of Psychopathology (HiTOP): A Quantitative Nosology Based on Consensus of Evidence," by R. Kotov, R. F. Krueger, D. Watson, D. C. Cicero, C. C. Conway, C. G. DeYoung, N. R. Eaton, M. K. Forbes, M. N. Hallquist, R. D. Latzman, S. N. Mullins-Sweatt, C. J. Ruggero, L. J. Simms, I. D. Waldman, M. A. Waszczuk, and A. G. C. Wright, 2021, May 7, *Annual Review of Clinical Psychology*, *17*(1), pp. 83–108 (https://doi.org/10.1146/annurev-clinpsy-081219-093304). Copyright © 2021 by Annual Reviews. Reprinted with permission. See the online article for the color version of this figure.

provide comprehensive coverage of psychopathology in terms of its clinical presentation. Indeed, many clinically important problems (such as narcissism, drunk driving, and suicide attempts) are outside the scope of these frameworks. The authors of RDoC were explicit that RDoC was not designed to replace current diagnostic systems or to be adopted in clinical practice (though it is certainly intended to produce discoveries that can inform advances in diagnosis and treatment; Kozak & Cuthbert, 2016). Further, the three frameworks include a number of legacy self-report measures that have suboptimal specificity, reliability, and validity (National Advisory Mental Health Council, 2016; Watson et al., 2017).

In contrast, HiTOP is designed to provide a comprehensive catalog of dimensions characterizing clinical manifestations of psychopathology and is ready for immediate clinical and research applications (Kotov et al., 2021, 2022; Ruggero et al., 2019). HiTOP can be operationalized with existing validated measures, including self-reports, informant reports, and interviews (and we encourage researchers to rely on multiple modalities when possible, given the biases inherent in single-informant ratings). Additionally, the consortium is developing new instruments tailored to the system that will be reliable, validated, and normed in the general population to allow interpretation of scores for individual patients (Kotov et al., 2022). Importantly, however, HiTOP is a descriptive system that classifies clinical phenomena without specifying their etiology or mechanisms. Hence, HiTOP complements RDoC, ANA, and NIDA PhAB in description and measurement of behavior but does not replace them.

HiTOP can also facilitate clinical application of the NIH frameworks by providing a crosswalk between clinical presentations and NIH constructs grounded in neuroscience. Though it does not specify etiology or mechanisms itself, HiTOP can aid NIH frameworks by providing dimensions that are valid, empirically coherent, and psychometrically robust clinical targets for genomic and neuroimaging studies (Latzman et al., 2020; Waszczuk et al., 2020). Reciprocally, research drawing on NIH frameworks can help validate HiTOP dimensions and explicate their biological underpinnings. Jointly, HiTOP and neuroscience-based frameworks may have the potential eventually to produce a unified nosology that rigorously characterizes both behavioral manifestations of psychopathology and their etiology.

Some linkages between HiTOP and NIH frameworks can already be identified. A recent comprehensive literature review examined empirical studies that correlated markers of the six RDoC domains and six HiTOP spectra, as well as more specific subdimensions within them (Michelini et al., 2021). The review identified many links between RDoC constructs or subconstructs and HiTOP dimensions, each supported by multiple studies. At the levels of RDoC domains and HiTOP

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spectra, several associations were particularly prominent in their effect size and consistency. These top links are shown in Figure 4.

Provisional connections of HiTOP with ANA and NIDA PhAB can be drawn based on the substantial overlap of their domains with RDoC, as indicated in Figure 4. Consequently, HiTOP constructs that are correlates of negative valence should also be correlates of negative emotionality; similarly, incentive salience should parallel positive valence, executive functions should parallel cognitive systems, and sleep should parallel the arousal/regulatory domain. Linking NIDA PhAB's interoception and metacognition domains to HiTOP requires additional investigation, but metacognition has apparent conceptual links to antagonistic externalizing (Watts et al., 2023).

Although the links in Figure 4 are not all one-to-one pairings, some specificity is apparent, as each NIH domain shows prominent associations with one to three HiTOP spectra. Links between more specific RDoC constructs and HiTOP dimensions are more complex, however. For example, although a connection between RDoC's positive valence and HiTOP's internalizing dimension is not apparent at the level of organization depicted in Figure 4, RDoC's initial response to reward construct (within positive valence) is negatively associated with HiTOP's distress subfactor (within internalizing). This pattern underscores the hierarchical nature of HiTOP and RDoC constructs. General levels offer a more parsimonious description, whereas more specific levels contribute additional valuable information and nuance. This flexibility allows studies to focus on the level most suitable to their goals (e.g., investigating neurocircuitry common to all internalizing disorders vs. neurocircuitry specific to anhedonia). In future research, studies using the NIH frameworks can include HiTOP-consistent assessments in order to elucidate the etiology and mechanisms of clinical phenomena and to identify and control for relevant patterns of comorbidity (Latzman et al., 2020).

The identified links between HiTOP and the NIH frameworks can be used to guide future research in clinical neuroscience or interpretation of existing research. For example, RDoC constructs can be used to deepen the interpretation of neuroscientific results for HiTOP dimensions, as we now illustrate using some of the results of our systematic review. Internalizing is primarily linked to negative valence, and the RDoC matrix shows that all but one construct within negative valence has been linked to extended amygdala function. This provides context in which to consider the mixed results for associations between internalizing and amygdala volume in our review (three significant findings and two failures to replicate). The RDoC matrix links the P300 waveform, consistently found to be negatively correlated with externalizing, with the construct attention in the cognitive domain, consistent with interpretations of this association as indicative of poor attentional control and with the link in Figure 4 between the cognitive domain and disinhibited externalizing.

At levels of HiTOP below the spectra, links to RDoC can also be informative. Our review suggests that distress is associated with reduced volume of the rostral ACC. RDoC links rostral ACC to fear (acute threat), whereas fear in HiTOP is a separate subfactor of internalizing, distinct from distress. However, RDoC links "dysregulation of cingulate reactivity" to sustained threat, which is a better match for distress. This contrast suggests an avenue for future research, probing more precisely what region of rostral ACC and what aspects of its function are linked to distress, not to mention whether the fear subfactor might also be related to parameters of rostral ACC.

We found mixed results for a negative association of depression with amplitude of the reward positivity, and here too RDoC is relevant, linking the reward positivity (though under its other name, the feedback-related negativity) to reward learning. Michelini et al. (2021) identified links of reward learning not only to harmful substance use but also to distress, the larger dimension of which depression is a symptom component. This suggests the potential utility of investigating other symptom components of distress for associations with the reward positivity. On the whole, these comparisons indicate that RDoC can be useful in dialogue with HiTOP-focused neuroimaging, sometimes providing evidence about the plausibility and meaning of findings and sometimes calling results into question and suggesting additional avenues of research to explore.

Using HiTOP in Clinical Neuroscience Research

Figure 5 illustrates the basic approach to using HiTOP in human clinical neuroscience research. Clinical phenotypes of interest are dimensions of psychopathology rather than categorical diagnoses. In place of case–control designs, participants are sampled from the general or treatment-seeking population to capture a range of variance in the dimensions of interest. Although sampling based on diagnostic categories is not recommended, oversampling individuals who fall at the high end of the dimension in question can be useful. In intervention research where treatment for a particular form of psychopathology is of interest, the aim would be to recruit participants with sufficient elevation on the corresponding HiTOP dimension (e.g., at least 1.5 *SD*s above the norm) to achieve measurable therapeutic benefit if the treatment is efficacious.

Case–control designs often create insurmountable confounds because healthy controls are likely to differ from cases in many ways beside the focal diagnosis, such as in socioeconomic status. Further, when people with the focal diagnosis are excluded for having comorbid diagnoses, the resulting case group is unlikely to be representative of the diagnostic category. In HiTOP-oriented research, researchers can use assessment of other HiTOP dimensions to control and investigate comorbidity statistically, and they can also employ statistical control of potential confounds like socioeconomic status (Tiego et al., 2023).

Widespread adoption of similar dimensional constructs and measures within clinical neuroscience would facilitate cumulative progress and pooling of data across research groups to enable well-powered investigation of complex data sets (Holmes & Patrick, 2018; Shackman & Fox, 2018). Additionally, this principle applies not only to the measurement of clinical phenomena organized by HiTOP but also to measurement of the brain. Analogous to the development of HiTOP as a consensus taxonomy of psychopathology is the movement toward consensus taxonomies of macroscale functional networks in the brain (Uddin et al., 2019, 2023). Neural variables that characterize these networks, their subnetworks, and the interactions among them are likely to be crucial for understanding psychopathology (van den Heuvel & Sporns, 2019). Harmonizing measures of both neural networks and HiTOP dimensions across research groups will allow for more effective mapping of HiTOP constructs to their neurobiological substrates.

When investigating HiTOP dimensions, researchers should keep in mind that various modeling strategies can be used to produce latent psychopathology variables, and choice of model may influence results. Many studies involving the p-factor have used confirmatory

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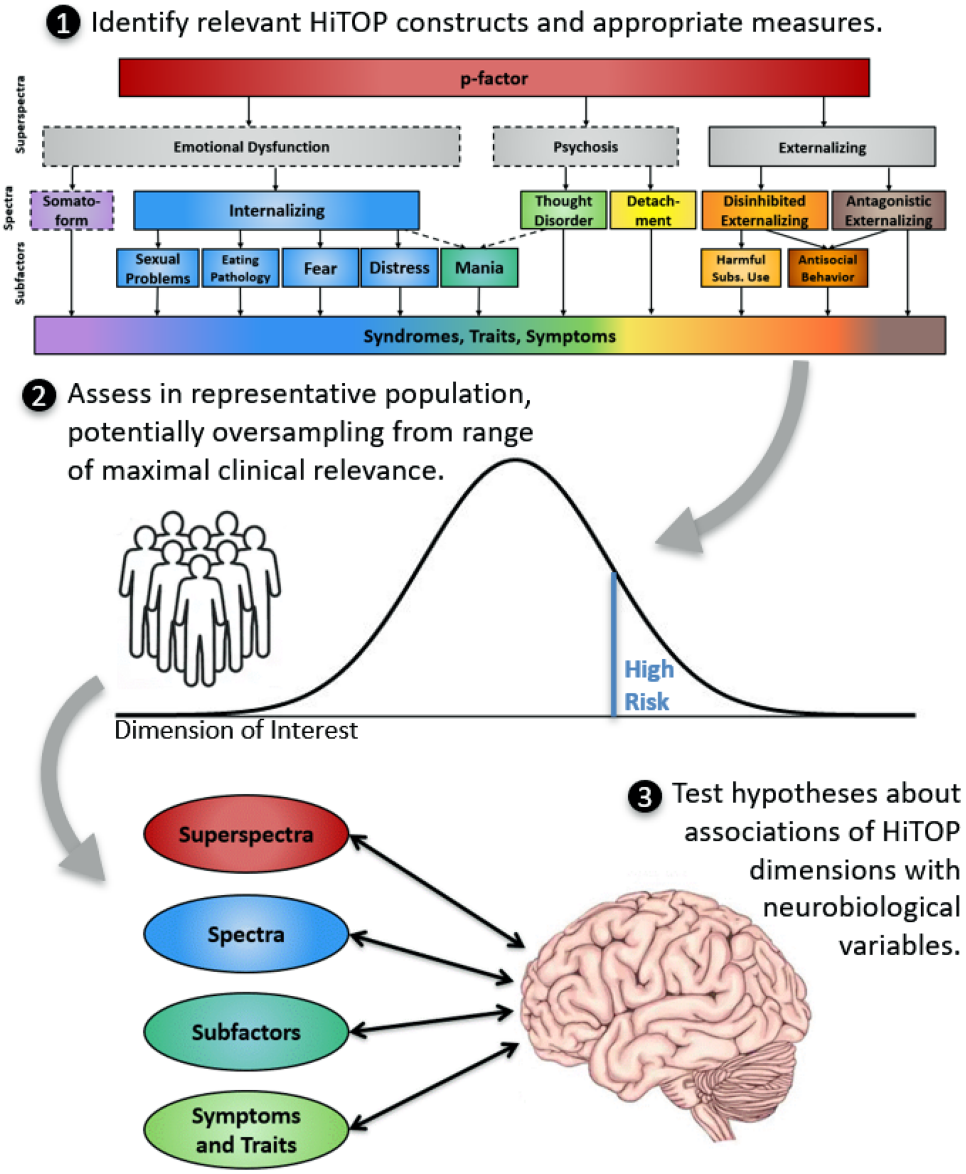
Figure 5

Using HiTOP in Clinical Neuroscience



Note. Step 1 involves selecting clinical phenotypes from HiTOP to study (figure depicts a simplified model; for full list of constructs, see Kotov et al., 2017, 2022). Optimal HiTOP measurement uses fully dimensional instruments without skip-outs and, if possible, with multiple assessment modalities (e.g., self- and informant reports and clinical interviews). Step 2 depicts a sampling design appropriate for HiTOP-based research, which involves sampling from transdiagnostic patient populations or the general population, rather than a case–control design. However, researchers may oversample participants manifesting or at high risk for the problems of interest. Step 3 depicts testing associations between HiTOP phenotypes and neurobiological variables, ideally examining nested constructs at multiple levels of the hierarchy and examining constructs from multiple spectra to assess discriminant validity. HiTOP = Hierarchical Taxonomy of Psychopathology; Subs. = substance. Adapted from "Using Empirically-Derived Dimensional Phenotypes to Accelerate Clinical Neuroscience: The Hierarchical Taxonomy of Psychopathology (HiTOP) Framework," by R. D. Latzman, C. G. DeYoung, and The HiTOP Neurobiological Foundations Workgroup, 2020, February 28, *Neuropsychopharmacology*, *45*(7), pp. 1083–1085 (https://doi.org/10.1038/s41386-020-0639-6). Copyright © 2020 by American College of Neuropsychopharmacology. See the online article for the color version of this figure.

bifactor models, but evidence is accumulating that such models are suboptimal, especially for studies that attempt to investigate specific, lower level factors in addition to the p-factor (Forbes et al., 2021; Watts et al., 2020). Although the depiction of HiTOP in Figure 1 resembles a higher order factor model, the figure need not be translated directly to any particular statistical model, and HiTOP does

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not dictate the choice of such models. Researchers may reasonably use various methods, including bifactor models fit with exploratory structural equation modeling, higher order models, or correlated-factor models. Researchers should keep in mind that when latent variable models are used to create estimated factor scores, those scores are often correlated with each other even when the factors in the latent model were uncorrelated. Correlated factor scores make it important to use other factors as covariates when attempting to ascertain factor-specific associations with neural variables.

One limitation of HiTOP is that it does not currently incorporate the development and change of features of psychopathology into its descriptive system. Nonetheless, it provides a useful framework of variables for studying change. To advance understanding of the etiology of HiTOP constructs, the use of research designs that facilitate causal inference will be crucial. Merely identifying neural correlates of HiTOP dimensions does not reveal whether those correlates are causes or consequences of dysfunction in the dimensions of interest, and causal processes are probably bidirectional (Perkins et al., 2020). For example, some longitudinal studies find that scores on dimensions of psychopathology predict later change in brain structure (Muetzel et al., 2018), whereas others find that patterns of neural variables predict later change in dimensions of psychopathology (Castellanos-Ryan et al., 2014). Longitudinal studies, genetically informative designs, and interventions targeting neural functioning using pharmacology, neurostimulation, or psychotherapy are needed to elucidate these causal relationships. Additionally, the computational-psychiatry and machine-learning approaches that are beginning to transform clinical neuroscience (Huys et al., 2016, Redish & Gordon, 2016) can also aid in identifying causal mechanisms and will benefit from the assessments that HiTOP can provide as clinical targets.

Connecting HiTOP to Research in Other Species

Thus far, we have focused on research on humans, but much clinical neuroscience is conducted using animal models, and such research can be pivotal in moving from correlational studies, like those we reviewed here, to studies of causal mechanism that are crucial for developing novel treatments. In animal models, recent methodological advances, such as optogenetics and single-cell RNA sequencing, make it possible to manipulate and measure the brain with unprecedented precision, creating vital opportunities for pinpointing the neural mechanisms—from molecules to macrocircuits—that underlie psychopathology. However, progress is impeded by the poor alignment between animal models and official diagnostic categories (Hyman, 2007). Most animal studies are models of specific symptoms (e.g., anhedonia) rather than of a diagnostic syndrome (e.g., major depressive disorder). Recognizing this disconnect, National Institute of Mental Health, National Institute on Alcohol Abuse and Alcoholism, and NIDA have increasingly organized their research portfolios around dimensional frameworks—RDoC, ANA, and NIDA PhAB—that encompass biologically tractable, transdiagnostic symptom dimensions. Additionally, we hope that the trend toward dimensional frameworks encourages researchers who study other species to pay attention to individual differences in their subjects.

HiTOP can complement these frameworks in research that involves animal models, just as it does in human neuroscience, by providing the link between laboratory discoveries and features of patients' clinical presentation. Correspondences between HiTOP dimensions and dimensions from the NIH frameworks (Michelini et al., 2021) enable improved mapping of findings in other species to human symptoms. For example, researchers studying constructs and neural circuits described by RDoC can use HiTOP to link their results to human symptoms that are likely to be relevant. Unlike categorical diagnoses, HiTOP creates a natural framework for linking mechanistic insights to psychopathology, and clinical neuroscientists should consider HiTOP dimensions as potential targets for animal models to link preclinical and clinical work more tightly. (Note that we were not suggesting that a hierarchical taxonomy of behavioral dimensions should be designed for other species. Rather, we are suggesting that the symptom dimensions identified by HiTOP are often easier to translate to dimensions of animal behavior than are traditional diagnostic categories.)

Research on anxiety, a symptom dimension core to internalizing, illustrates the utility of HiTOP-concordant phenotypes in animal research. Pathological anxiety is both prevalent and debilitating, but existing treatments are ineffective for many people, and side effects can be debilitating. Hence, developing a clearer understanding of the neural systems governing anxiety is urgent, and controlled manipulations of neural function enabled by animal models are essential for pinpointing the mechanisms that are necessary and sufficient for orchestrating specific manifestations of anxiety (e.g., behavioral inhibition). Work in nonhuman primates has proven especially valuable for identifying the specific neural mechanisms underlying persistent individual differences in anxious temperament. Using a combination of large multigenerational samples, multimodal neuroimaging, molecular genetics, and targeted perturbation studies, this research has (a) identified a distributed cortico-subcortical network (involving the extended amygdala, anterior hippocampus, orbitofrontal cortex, anterior insula, and periaqueductal gray) associated with stable individual differences in anxious temperament, (b) discovered candidate molecular pathways, and (c) determined the heritability and causal contributions of specific regional and molecular components (Fox & Shackman, 2019; Fox et al., 2015; Kenwood & Kalin, 2021). HiTOP provides a map of the features of psychopathology to which this research on anxiety is most likely to be relevant, suggesting that anxious temperament contributes to symptoms encompassed by the internalizing spectrum, such as social anxiety, separation insecurity, phobias, and features of generalized anxiety (Kotov et al., 2017; Watson et al., 2022).

HiTOP can also help to lay the groundwork for reorganizing therapeutics development and regulation around transdiagnostic psychiatric symptoms. Translational research on anhedonia—a loss of sensitivity to rewards often associated with depression—provides an excellent example. Rodent research has identified the κ-opioid receptor as a target for altering behaviors associated with deficits in reward processing (Pizzagalli et al., 2020). An 8-week, double-blind, placebo-controlled, randomized trial of a κ-opioid antagonist showed effectiveness in increasing reward processing in human patients selected using a dimensional measure of anhedonia (Krystal et al., 2020; Pizzagalli et al., 2020). HiTOP's placement of anhedonia indicates that this research is likely to be relevant to features of psychopathology associated with the detachment and internalizing spectra (Kotov et al., 2017, 2020; Watson et al., 2022).

Typical translational research in animal models pairs a manipulation with some specific behavioral outcome. The behaviors are almost always transdiagnostic, which is in keeping with HiTOP, and they are usually narrow, corresponding to constructs from lower levels of HiTOP (e.g., anxiety and anhedonia). However, the manipulations

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(e.g., stress or gene knockouts) often affect a range of behaviors, and so they may be interpretable in the context of higher level HiTOP constructs, such as spectra, that encompass a range of symptoms. HiTOP thus provides a potentially powerful organizing framework for research linking animal models to the clinical manifestations of human psychopathology at multiple levels of generality. By encouraging the use of psychometrically sound, dimensional constructs and locating them in relation to other features of psychopathology, HiTOP may accelerate the development of effective biological interventions.

Conclusion

Lacking a quantitative and validated guiding nosological model, progress in clinical neuroscience has been difficult. Neuroscientific evidence increasingly shows that many of the biological correlates of mental illness are transdiagnostic, corresponding to symptom dimensions cutting across traditional diagnoses. Prior to the development of HiTOP, however, there was no system capable of organizing the full range of dimensional clinical phenotypes. Our review of 164 neuroimaging studies not only identifies some promising replicated findings but also illustrates how HiTOP provides a framework for linking clinical phenotypes with measures of neurobiological systems. HiTOP allows integration of a comprehensive clinical description with the various biobehavioral constructs targeted by clinical neuroscientists and NIH initiatives. We predict HiTOP will play an important role in the discovery of the neurobiological mechanisms underlying different forms of psychopathology.

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