Validity and utility of Hierarchical Taxonomy of Psychopathology (HiTOP): III. Emotional dysfunction superspectrum

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The Hierarchical Taxonomy of Psychopathology (HiTOP) is a quantitative nosological system that addresses shortcomings of traditional mental disorder diagnoses, including arbitrary boundaries between psychopathology and normality, frequent disorder co-occurrence, substantial heterogeneity within disorders, and diagnostic unreliability over time and across clinicians. This paper reviews evidence on the validity and utility of the internalizing and somatoform spectra of HiTOP, which together provide support for an emotional dysfunction superspectrum. These spectra are composed of homogeneous symptom and maladaptive trait dimensions currently subsumed within multiple diagnostic classes, including depressive, anxiety, trauma-related, eating, bipolar, and somatic symptom disorders, as well as sexual dysfunction and aspects of personality disorders. Dimensions falling within the emotional dysfunction superspectrum are broadly linked to individual differences in negative affect/neuroticism. Extensive evidence establishes that dimensions falling within the superspectrum share genetic diatheses, environmental risk factors, cognitive and affective difficulties, neural substrates and biomarkers, childhood temperamental antecedents, and treatment response. The structure of these validators mirrors the quantitative structure of the superspectrum, with some correlates more specific to internalizing or somatoform conditions, and others common to both, thereby underlining the hierarchical structure of the domain. Compared to traditional diagnoses, the internalizing and somatoform spectra demonstrated substantially improved utility: greater reliability, larger explanatory and predictive power, and greater clinical applicability. Validated measures are currently available to implement the HiTOP system in practice, which can make diagnostic classification more useful, both in research and in the clinic.

Key words: HiTOP, emotional dysfunction, internalizing, somatoform, depression, anxiety disorders, eating disorders, sexual dysfunction, negative affect, neuroticism, clinical utility

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The Hierarchical Taxonomy of Psychopathology (HiTOP) uses data from studies on the organization of psychopathology to construct a quantitative nosological system[1-4]. The HiTOP organizes psychopathology into a multilevel hierarchical structure. Hierarchical structures connect phenomena representing varying levels of specificity, i.e., a broader dimension at one level can be decomposed into more specific dimensions at lower levels. The broader dimension represents shared features that produce a correlation between the more specific dimensions; however, these specific variables still contain their own unique aspects and can be differentiated at a more fine-grained level. For example, diagnoses of major depressive disorder (MDD) and generalized anxiety disorder (GAD) tend to co-occur in individuals and, therefore, are strongly correlated with one another[2,5-7]. Consequently, they both can be subsumed within broader dimensional constructs, such as distress disorders[2,4]. However, MDD and GAD have distinctive features that need to be modeled in any comprehensive structure.

The lower levels of the HiTOP hierarchy contain specific, homogeneous symptom dimensions (e.g., insomnia) and maladaptive traits (e.g., irritability). These homogeneous elements can be combined into dimensional syndromes, some of which roughly correspond to traditional diagnoses such as MDD and GAD. Similar syndromes are combined into subfactors, such as the class of distress disorders that includes MDD and GAD. Larger constellations of syndromes form broader spectra, such as internalizing. Finally, these spectra can be aggregated into extremely broad superspectra, ultimately leading to a general factor of psychopathology[2,8-10].

The HiTOP currently includes six spectra[2]. These spectra can be conceptualized as forming three superspectra: psychosis (combining thought disorder and detachment), externalizing (subsuming disinhibited and antagonistic forms of psychopathology), and emotional dysfunction (modeling the commonality between internalizing and somatoform). Although these superspectra were not formalized in the original HiTOP system, they are supported by evidence reviewed in a series of papers published in this journal. The first paper[11] focused on the psychosis superspectrum, whereas the second[12] examined externalizing; this paper discusses the emotional dysfunction superspectrum.

The HiTOP model resolves widely recognized problems of traditional nosologies. First, traditional taxonomies consider

mental disorders to be discrete categories, whereas the data show that virtually all major forms of psychopathology exist on a continuum with normality[13-19]. Consequently, systems based on dichotomous diagnoses lead to a substantial loss of clinically significant information[14,20-22]. Most notably, many patients fall short of the criteria for any disorder, despite experiencing clinically significant impairment. The HiTOP solves this problem by assessing psychopathology as a series of continuous dimensions. No patients are excluded from the system, because even those with subthreshold or atypical symptoms can be characterized on a comprehensive set of dimensions. Moreover, dimensions capture clinically important differences in symptom severity among individuals who do meet criteria for a disorder[14].

Second, dichotomous diagnoses show limited reliability, both over time and across clinicians[23-25]. For instance, the DSM-5 field trials found that many common diagnoses – including MDD (kappa = .28) and GAD (kappa = .20) – did not meet even a relaxed cutoff for acceptable interrater reliability[25]. Again, the HiTOP addresses this problem by modeling psychopathology dimensionally: extensive evidence establishes that the same clinical phenomena are much more reliable when assessed continuously[22,26-30].

Third, many diagnoses are heterogeneous and encompass diverse characteristics[6,14,31,32]. This problem is exacerbated by the fact that current nosological systems make ample use of polythetic diagnoses, such that a patient only needs to meet a specified number of criteria to have a disorder. For example, a patient needs to meet only five of nine criteria to be diagnosed with MDD in the DSM-5[33], which means that there are 227 possible ways to receive this diagnosis[32]; this number increases to 16,400 if one takes into account different symptom presentations within criteria (e.g., insomnia vs. hypersomnia)[34]. Post-traumatic stress disorder (PTSD) represents an extreme example of the combinatorial problem with polythetic diagnoses, given that there are 636,120 possible ways to receive this DSM-5 diagnosis[35]. Consequently, patients with the same diagnosis can present with very different problems and may have few – if any – overlapping symptoms[34,36]. The HiTOP addresses this problem by decomposing broader syndromes into homogeneous dimensions at lower levels of the hierarchy.

Fourth, comorbidity is a pervasive problem in traditional taxonomies[5-7,37-43]. We already have noted the strong comorbidity between MDD and GAD. High comorbidity suggests that unitary conditions have been split (perhaps arbitrarily) into multiple diagnoses, which co-occur frequently in individuals as a result. The HiTOP addresses this problem by modeling comorbidity directly. Indeed, the HiTOP structure essentially represents empirical patterns of correlations/comorbidity, i.e., strongly correlated conditions are placed near to one another (e.g., in the same spectrum), whereas less strongly related phenomena are located farther apart (e.g., in different spectra). This hierarchical system is highly flexible, such that clinicians and researchers can focus on whatever level is most informative for a given problem[2,44].

In this paper, we examine the HiTOP emotional dysfunction superspectrum. As noted, this superspectrum represents the commonality of the internalizing and somatoform spectra.

STRUCTURAL EVIDENCE

Internalizing spectrum

Internalizing is the largest and most complex of the HiTOP spectra. It consistently emerges as a distinct spectrum in structural analyses. However, the composition of this spectrum is critically dependent on the specific variables included in the analysis. Table 1 summarizes findings from the large number of studies that have modeled internalizing using diagnostic data[8,9,45-87]. Internalizing clearly subsumes a very broad range of psychopathology, including content related to depressive disorders, anxiety disorders, obsessive-compulsive and related disorders, trauma- and stressor-related disorders, eating disorders, and personality disorders.

Several subfactors have been identified within internalizing. Table 1 presents findings related to the two broadest and best replicated subfactors[2]. First, the distress subfactor includes disorders that involve pervasive negative emotionality[6], such as MDD, dysthymic disorder, GAD and PTSD. Second, the fear subfactor is defined by disorders that involve more specific, context-delimited forms of distress and that frequently include behavioral avoidance, such as panic disorder, agoraphobia, social phobia, and specific phobia. These distress and fear subfactors are strongly correlated, and some studies have found them to be indistinguishable[47,52,67]. Relatedly, some diagnoses – such as obsessive-compulsive disorder (OCD) – do not fall clearly into either subfactor.

Growing evidence indicates that eating pathology forms a third subfactor within internalizing[2,77,78,88], although it is sometimes included in the distress subfactor (Table 1). At the syndrome level, this cluster is defined by disorders such as bulimia nervosa, anorexia nervosa, and binge eating disorder[77,78]. At the symptom level, structural/psychometric evidence has established the existence of eight specific dimensions: body dissatisfaction, binge eating, cognitive restraint, purging, excessive exercise, restricting, muscle building, and negative attitudes toward obesity. These eight dimensions have been replicated across a variety of populations[89-92].

Evidence has also emerged for a fourth subfactor of sexual problems[2,93-95]. This cluster is defined by multiple symptoms of sexual dysfunction, including low sexual desire, difficulties with arousal, low orgasmic function, and sex-related distress.

Finally, several studies have found that indicators of mania/bipolar disorder fall within the internalizing spectrum and often help to define its distress subfactor. However, other studies have linked mania to the thought disorder spectrum[8,47,49]. Accordingly, mania is currently an interstitial construct in HiTOP, with important connections to both internalizing and thought disorder. Mania subsumes several distinct symptom dimensions, including emotional lability, euphoric activation, hyperactive cognition, reckless overconfidence, and irritability[96-100]. These symptom dimensions have distinctive correlates, and more fine-grained analyses will likely reveal that they are located in different HiTOP spectra.

Table 1 Structural evidence on the internalizing spectrum

	N	Sample type	DEP	DYS	GAD	PTSD	PAN	AGO	SOC	SPE	OCD	BPD	MAN	SAD	AN	BN	BED	PSY
Internalizing																		
Dunedin Study (Caspi et al[8], Krueger et al[45])	1,037	Community/ longitudinal	+	+	+		+	+	+	+	+							
MIDAS (Forbes et al[46], Kotov et al[47])	2,900	Outpatients/adults	+		+	+	+		+	+	+	+	–		+	+	+	–
NCS (Levin-Aspenson et al[48])	8,098 & 5,877	Community/adults	+	+	+	+	+	+	+	+			+					+/–
NESARC (Keyes et al[49], Kim & Eaton[50])	43,093 & 34,653	Community/adults	+	+	+	+	+	+	+	+			+					
Norwegian Twin Panel (Kendler et al[51], Røysamb et al[52])	2,794	Community/adults	+	+/–	+	+	+	+	+/–	+		+/–			+			
WMH Surveys (Kessler et al[53])	21,229	Community/ longitudinal	+	+	+	+	+	+	+	+	+		+	+				
Conway & Brown[54]	4,928	Outpatients/adults	+	+	+	+	–		+	–	–	–	–					
Conway et al[55]	25,002	University/adults	+	+	+	+	+		+	+	+		–		+	+	+	
Conway et al[56]	815	Community/ longitudinal	+	+	+	+	+		+									
Farmer et al[57]	816	Community/ longitudinal	+	+	+	+	+		+	+			+	+		+		
Girard et al[58]	825	Mixed/adults	+	–	–	+	+					+						
King et al[59]	1,329	Community/young adults	+		+	+	+		+	–								
Kotov et al[60]	469	Inpatients/adults	+				+		+		+							
Martel et al[61]	2,512	Community/ children	+		+		+	+	+	+	+			+	+	+	+	
Martel et al[61]	8,012	Community/adults	+		+		+	+	+	+	+		+	+				+
Olino et al[62]	541	Community/ children	+		+		+	–	–	–				+				
Schaefer et al[63]	2,232	Community/ adolescents	+		+	+									+	+		
Scott et al[64]	156	Community/young women	+	+	+	+	+		+	+		+						
Verona et al[65]	4,745	Community/adults	+		+		+			+	+		+					+
Verona et al[66]	223	Mixed/youth	+		+													
Wright & Simms[67]	628	Outpatients/adults	+	+	+	+	+		+		–	+						–
Total positive			21/21	10.5/12	19/20	14/14	18/19	7/8	15.5/17	12/15	8/10	4.5/6	6/9	5/5	5/5	5/5	3/3	2.5/5

Table 1 Structural evidence on the internalizing spectrum *(continued)*

	N	Sample type	DEP	DYS	GAD	PTSD	PAN	AGO	SOC	SPE	OCD	BPD	MAN	SAD	AN	BN	BED	PSY
Distress																		
EDSP (Beesdo-Baum et al[68], Wittchen et al[69])	3,021	Community/ longitudinal	+	+	+				+		+		+		+	+	+	
NCS (Cox et al[70], Krueger[71], Levin-Aspenson et al[48])	8,098 & 5,877	Community/adults	+	+	+	+/–	+/–	+/–	–	–			+/–					+/–
NESARC (Eaton et al[72,73], Keyes et al[74], Kim & Eaton[50], Lahey et al[9])	43,093 & 34,653	Community/adults	+	+	+	+	+/–		+/–	–		+	+					
WMH Surveys (de Jonge et al[75])	21,229	Community/ longitudinal	+	+	+	+										+	+	
Blanco et al[76]	9,244	Community/ adolescents	+	+	+	+							+	+	+	+	+	
Conway et al[55]	25,002	University/adults	+	+	+	+							–					
Forbush & Watson[77]	16,423	Community/adults	+	+	+	+	–	–	–	–		–	–		–	–	–	
Forbush et al[78]	1,434	Community/ longitudinal	+	+														
James & Taylor[79]	1,197	Community/adults	+	+	+							+						
Kotov et al[80]	385 & 288	Mixed/adults	+		+	+	+	–	–	–	–		–					
Martel et al[61]	2,512	Community/ children	+		+						+				+	+	+	
Martel et al[61]	8,012	Community/adults	+		+						+		+					+
Miller et al[81]	1,325	Veterans/adults	+			+												
Miller et al[82]	214	Veterans/adults	+	+	+							+						
Mitchell et al[83]	760	Mixed/adults	+	+	+										+/–	+	+	
Slade & Watson[84]	10,641	Community/adults	+	+	+	+												
South et al[85]	1,858	Community/adults	+		+													
Vollebergh et al[86]	7,076	Community/adults	+	+	+													
Wright et al[87]	8,841	Community/adults	+		+	+	+						+					
Total positive			19/19	13/13	17/17	9.5/10	3/5	0.5/3	1.5/5	0/4	3/4	3/4	5.5/9	1/1	3.5/5	5/6	5/6	1.5/2
Fear																		
EDSP (Beesdo-Baum et al[68], Wittchen et al[69])	3,021	Community/ longitudinal					+	+	+/–	+								

Table 1 Structural evidence on the internalizing spectrum *(continued)*

	N	Sample type	DEP	DYS	GAD	PTSD	PAN	AGO	SOC	SPE	OCD	BPD	MAN	SAD	AN	BN	BED	PSY
NCS (Cox et al[70], Krueger[71], Levin-Aspenson et al[48])	8,098 & 5,877	Community/adults	+/–	–	+/–	+/–	+	+	+	+			+/–					–
NESARC (Eaton et al[72,73], Keyes et al[74], Kim & Eaton[50], Lahey et al[9])	43,093 & 34,653	Community/adults	–	–	+/–	+	+	+	+	+			–					
WMH Surveys (de Jonge et al[75])	21,229	Community/ longitudinal					+	+	+	+								
Blanco et al[76]	9,244	Community/ adolescents					+	+	+	+								
Conway et al[55]	25,002	University/adults					+		+	+	+							
Forbush & Watson[77]	16,423	Community/adults	–	–	–	–	+	+	+	+		–	–		–	–	–	
Forbush et al[78]	1,434	Community/ longitudinal							+	+								
James & Taylor[79]	1,197	Community/adults					+		+									
Kotov et al[80]	385 & 288	Mixed/adults	–		–	–	–	+	+	+	+		–					
Martel et al[61]	2,512	Community/ children					+	+	+	+				+				
Martel et al[61]	8,012	Community/adults					+	+	+	+				+				
Miller et al[81]	1,325	Veterans/adults					+	+			+							
Miller et al[82]	214	Veterans/adults					+	+		+	+							
Mitchell et al[83]	760	Mixed/adults					+	+		+	+							
Slade & Watson[84]	10,641	Community/adults					+	+	+		+							
South et al[85]	1,858	Community/adults					+		+	+								
Vollebergh et al[86]	7,076	Community/adults					+	+	+	+								
Wright et al[87]	8,841	Community/adults					+	+	+									
Total positive			0.5/4	0/3	1/4	1.5/4	17/18	15/15	15.5/16	15/15	6/6	0/1	0.5/4	2/2	0/1	0/1	0/1	0/1

+: indicator included in analysis and loaded ≥.30, –: indicator included in analysis but loaded <.30, +/–: inconsistent loadings across models or individual studies (counted as 0.5 in the total), DEP – major depression, DYS – dysthymia, GAD – generalized anxiety disorder, PTSD – post-traumatic stress disorder, PAN – panic, AGO – agoraphobia, SOC – social phobia, SPE – specific phobia, OCD – obsessive-compulsive disorder, BPD – borderline personality disorder, MAN – mania, hypomania or bipolar disorder, SAD – separation anxiety disorder, AN – anorexia nervosa, BN – bulimia nervosa, BED – binge-eating disorder, PSY – psychotic disorder, MIDAS – Methods to Improve Diagnostic Assessment and Services, NCS – National Comorbidity Survey, NESARC – National Epidemiologic Survey on Alcohol and Related Conditions, WMH – World Mental Health, EDSP – Early Developmental Stages of Psychopathology

Somatoform spectrum

Somatoform is currently the most tentative of the HiTOP spectra[2]. Early evidence suggested that somatoform psychopathology was subsumed within internalizing, based on data that somatization, hypochondriasis and neurasthenia loaded with depression and anxiety on a broader internalizing factor[101,102]. However, subsequent research has shown that, when a sufficient set of indicators is available, the somatoform spectrum is indeed separate from internalizing as well as the other HiTOP spectra[46,47,102,103,105,107-117]. These seemingly divergent sets of findings can easily be reconciled. Several studies[46,104,106] have demonstrated convincingly that internalizing and somatoform do form a single spectrum at very broad levels of the hierarchy, but, as one moves further down in levels of abstraction, somatoform separates from internalizing.

Table 2 lists 16 studies[46,47,102,103,106-117] conducted across a diverse range of countries – and using a wide range of populations and measurement modalities – that have yielded support for a higher-order somatoform factor. The indicators have mostly represented an array of bodily distress symptoms (e.g., pain, gastrointestinal, cardiopulmonary, chronic fatigue, functional neurological), akin to the bodily distress syndrome proposed by Fink and colleagues[118,119]. Although the broader categorical hypochondriasis diagnostic construct has loaded on the somatoform factor in the two studies in which it was included, this construct is multifactorial in nature[120]; it therefore would be important to determine the degree to which the components of cognitive preoccupation, bodily perceptions, reassurance seeking, and hypochondriacal worry load on this somatoform factor. Indeed, absent from all these studies are specific indicators reflecting health anxiety, which clearly includes aspects of both internalizing (i.e., anxious apprehension and fearfulness) and somatoform (i.e., somatic preoccupation and disease conviction) pathology. Future studies need to elucidate the placement of health anxiety in the hierarchy.

Role of maladaptive traits

Negative affect/neuroticism (NA/N) is a fundamental trait domain in research on personality and personality pathology. It also is a key part of the DSM-5 alternative model of personality disorders, as well as a trait qualifier in the new ICD-11 personality disorder diagnosis[121]. NA/N cuts across and ties together propensities to experience diverse negative emotional experiences – because these experiences are highly correlated – and thereby represents the central feature of internalizing. Indeed, cross-sectional data show that individual differences in broadly conceptualized internalizing psychopathology and NA/N are very highly correlated and essentially fungible[121-123].

NA/N is a higher-order dimension that subsumes many more specific facets, which are also strongly related to various forms of internalizing. Specific facets of NA/N include anxiousness, depressivity, anger/irritability, separation insecurity, and emotional lability[2,124-126], as well as social cognitive vulnerabilities such as anxiety sensitivity, self-criticism, rumination, hopelessness, and perfectionism. It is noteworthy that these social cognitive vulnerabilities show unique associations with internalizing syndromes[127-130]. For example, anxiety sensitivity is associated with panic and other syndromes, net of the general NA/N association with internalizing[128]. In addition, other major personality domains act synergistically with NA/N to affect the likelihood of experiencing specific forms of internalizing. For example, extraversion and conscientiousness mitigate the impact of NA/N on specific internalizing syndromes, such as depression[131,132].

NA/N traits also are predictive of future episodes of internalizing disorders[133-135]. Indeed, NA/N can be simultaneously conceptualized as a vulnerability for internalizing disorder, sharing causes with internalizing disorder, and lying within the same spectrum of human variation as internalizing disorder[136,137]. These connections may emerge from dynamic processes in which NA/N enhances stress, promoting internalizing symptomatology, and feeding back on general stress reactivity to further reinforce NA/N tendencies[138,139].

The strong association between NA/N and internalizing has led to a focus on articulating shared mechanisms and specific points of continuity[137]. Twin research shows that the close phenotypic overlap of NA/N and internalizing psychopathology is undergirded by shared genetic risk factors[140,141]. Distally, emerging molecular evidence also points to a genetic basis for NA/N-internalizing connections[142]. More proximally, shared neurocircuitry linking neuroticism to emotional dysregulation may constitute some of the manifest mechanisms underlying close NA/N-internalizing connections[143].

Finally, NA/N is broadly related to health complaints and somatic symptoms[144]; in fact, some models include somatic complaints as a specific facet within this domain[125,145]. NA/N has also been shown to be substantially associated with overreporting of health complaints[144], medically unexplained symptoms[146-149], health anxiety and hypochondriasis[120,150-156], and somatization/somatization disorder[157-160].

NA/N is broadly related to the symptoms, traits and disorders subsumed within the somatoform spectrum and, therefore, is partly responsible for its emergence in structural studies. Because NA/N is also broadly linked to the internalizing spectrum, it further helps to explain the existence of the emotional dysfunction superspectrum[161], which reflects important commonalities between somatoform and internalizing psychopathology.

Overall model

Figure 1 summarizes the proposed model of the emotional dysfunction superspectrum and its constituent spectra. The sections for internalizing and somatoform build upon the current HiTOP model[2] in light of the literature reviewed in this paper – in particular, highlighting those areas whose placement within this superspectrum is ambiguous or tentative. The model also includes illustrative symptom and trait dimensions that populate the lower levels of the hierarchy; these are taken from Kotov et al[2] and subsequent studies.

Internalizing consistently emerges as a distinct dimension in

Table 2 Structural evidence on the somatoform spectrum

	N	Sample type	Measure	General malaise	Pain	Neurological	Gastrointestinal	Fatigue	Cardiopulmonary	Somatic anxiety	Hypochondriasis
Cano-García et al[107]	1,255	Primary care	PHQ-15		+		+	+	+		
Budtz-Lilly et al[108]	2,480	Primary care	BDS Scale	+	+		+		+		
Deary[109]	315	Mixed	DSM-III-R questionnaire	+	+		+	+		+	
Gierk et al[110]	2,510	Community	SSS-8		+		+	+	+		
Leonhart et al[111]	2,517 456, 1,329	Routine clinical care General hospital	PHQ-15		+		+	+	+		
Marek et al[103]	810 533	Spine surgery patients Spinal cord stimulator patients	MMPI-2-RF	+	+	+	+			–	
McNulty & Overstreet[112]	925 1,199	Outpatient psychiatric Inpatient psychiatric	MMPI-2-RF	+,+	+,+	+,+	+,+			+,–	
MIDAS (Forbes et al[46], Kotov et al[47])	2,900	Outpatient psychiatric	SCID-I	+	+						+
Schmalbach et al[113]	2,386	Community	BDS Scale	+	+		+		+		
Sellbom[105]	895 42,290	Outpatient psychiatric Inmates	MMPI-2-RF	+,+	+,+	+,+	+,+			+,–	
Simms et al[102]	5,433	Primary care	CIDI	+		+					+
Thomas & Locke[114]	399	Epilepsy/NES patients	MMPI-2-RF	+	+	+	+				
Walentynowicz et al[115]	1,053	University	PHQ-15		+		+	+	+		
Witthöft et al[116]	414 308	Community Primary care	PHQ-15		+		+	+	+		
Witthöft et al[117]	1,520 3,053	University	PHQ-15		+		+	+	+		
Total positive				11/11	16/16	7/7	15/15	7/7	8/8	3/6	2/2

+: indicator included in analysis and loaded ≥.30, –: indicator included in analysis but loaded <.30, MIDAS – Methods to Improve Diagnostic Assessment and Services, PHQ-15 – Patient Health Questionnaire-15, BDS Scale – Bodily Distress Syndrome Scale, SSS-8 – Somatic Symptom Scale-8, MMPI-2-RF – Minnesota Multiphasic Personality Inventory-2 Restructured Form, SCID-I – Structured Clinical Interview for DSM-IV Axis I Disorders, CIDI – Composite International Diagnostic Interview, NES – non-epileptic seizures. General malaise includes undifferentiated somatoform symptoms, somatic depression, cognitive symptoms; pain includes fibromyalgia, musculoskeletal symptoms; neurological includes neurasthenia, conversion disorder; somatic anxiety includes physiological symptoms of anxiety (not health anxiety).

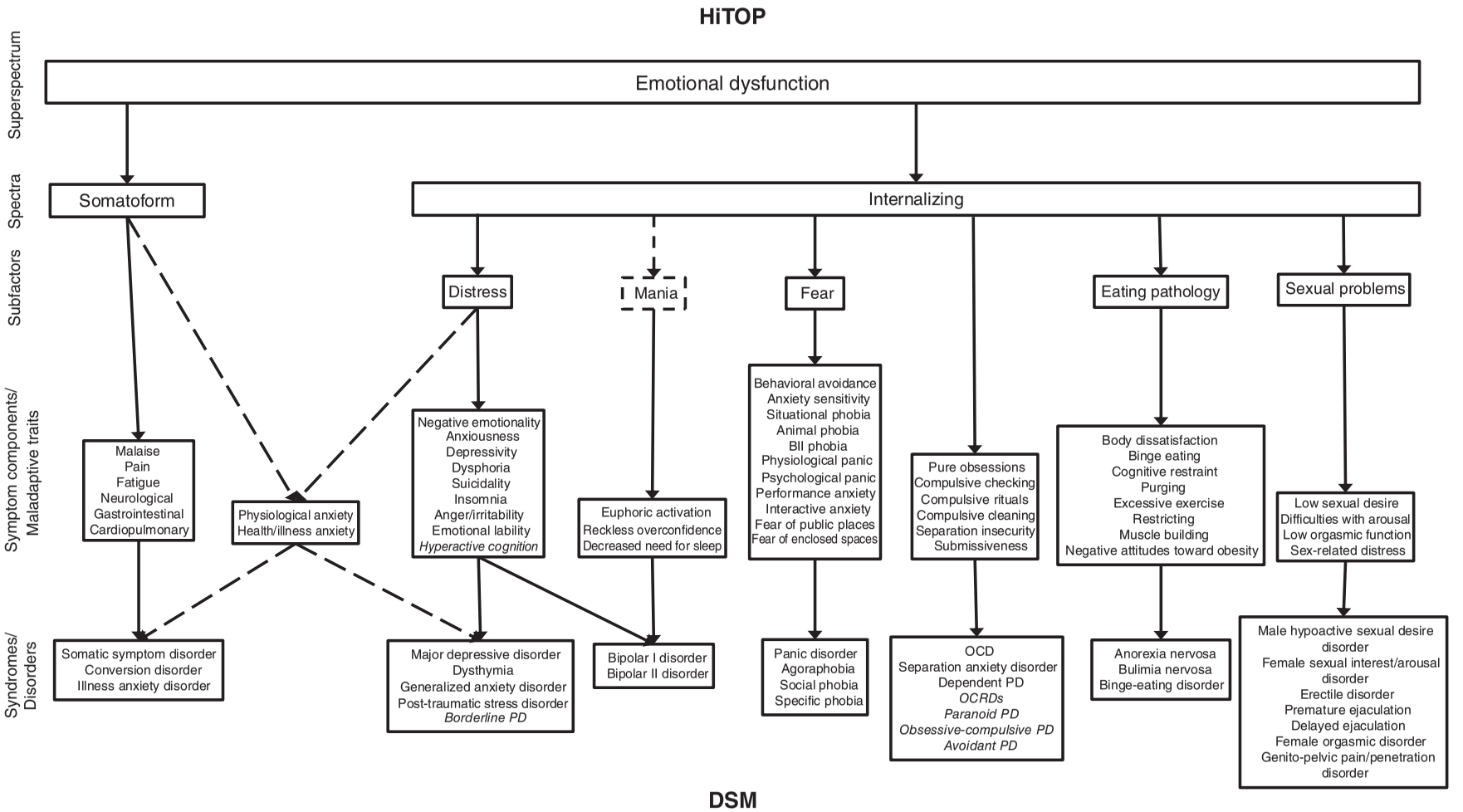

Figure 1 Conceptual model of the emotional dysfunction superspectrum. Dashed lines represent provisional inclusion. Symptom components and diagnoses with ambiguous or inconsistent structural placement are italicized. HiTOP – Hierarchical Taxonomy Of Psychopathology, PD – personality disorder, BII phobia – blood-injection-injury phobia, OCD – obsessive-compulsive disorder, OCRDs – obsessive-compulsive and related disorders

structural models, but its boundaries are unclear. For example, internalizing is strongly characterized by personality pathology related to NA/N[121-123]. However, personality disorders that load on internalizing (e.g., borderline and avoidant) often cross over into other spectra (externalizing and detachment, respectively[46,58]).

Table 1 demonstrates substantial support for subdividing internalizing into distress and fear subfactors, but evidence for the distress-fear distinction is not universal[46,52,55,56,67]. Some studies have found evidence for additional subfactors of internalizing, including sexual problems[93-95] and eating pathology[77,78], although eating pathology may form a separate structural dimension[55].

The somatoform spectrum is defined by a wide array of somatic complaints, as well as preoccupation with bodily symptoms. Somatoform problems covary substantially with internalizing psychopathology[52] and, as with internalizing, somatoform psychopathology is strongly associated with individual differences in NA/N[144]. Nevertheless, a somatoform spectrum can be distinguished from the internalizing one if a sufficient set of indicators is available[46,103,105].

VALIDITY EVIDENCE

Behavioral genetics

Twin studies suggest that the internalizing domain is moderately heritable and under shared genetic influences[51,140,141,162-167]. A substantial proportion of these genetic influences is also shared with externalizing, but the remaining vulnerability is specific to the internalizing spectrum. Importantly, these studies usually defined the internalizing spectrum as emotional problems, and the strongest genetic loadings were for MDD and GAD[163]. Within this narrower conceptualization of internalizing, there is evidence for separate genetic influences on distress and fear[168-170].

No study has examined genetic and environmental influences on all of the symptoms and traits subsumed within internalizing. However, it is possible to piece together how different HiTOP internalizing syndromes are genetically related from the research that does exist across different combinations of disorders. Multiple forms of eating pathology have common genetic vulnerability[171-173]. Moreover, twin studies indicate a shared genetic risk for eating pathology and emotional problems, including anxiety and depression symptoms[51,174-177]. There is also a substantial genetic correlation between anorexia nervosa and OCD[178]. Finally, twin and family studies indicate a partial genetic overlap between mania and unipolar depression[179-181], although the genetic association between mania and schizophrenia is substantially stronger[182-185]. Overall, there is prominent genetic overlap between different conditions within internalizing – except for mania – although there is no research on the genetic overlap with sexual problems.

In contrast, twin studies suggest that a significant proportion of genetic influences on somatoform spectrum symptoms are independent from internalizing problems[186,187]. For example, a common genetic factor contributes to four somatic symptoms: recurrent headache, irritable bowel syndrome, chronic impairing fatigue, and chronic widespread pain[188], independent of genetic influences shared with MDD and GAD. Nonetheless, the somatoform and internalizing spectra may share genetic underpinnings at a higher level of generality[51,186-191].

Overall, twin studies support shared genetic influences on the internalizing spectrum that are partially distinct from the genetic etiology of the somatoform spectrum. Future twin studies should assess a wider range of variables to test the genetic architecture comprehensively.

Molecular genetics

Genome-wide association studies (GWAS) detect genetic variants across the entire genome and allow one to compute molecular genetic correlations between traits[192]. Many genetic variants, each with a small effect size, have been found to contribute to the shared risk for internalizing. For example, depression shows high genetic correlations with generalized anxiety, NA/N, anhedonia, and PTSD (r_g>0.70)[193-196], as well as much smaller but significant genetic correlations with bipolar disorder, OCD, and anorexia nervosa (r_g=0.17-0.36)[197].

Genomic structural equation modeling (SEM) is another technique for investigating shared genetic influences across related conditions. It can extract common genetic dimensions from a set of molecular genetic correlations, and is thus useful for testing the genome-wide architecture of psychopathology. Using this approach, Waldman et al[198] identified a genetic internalizing factor, characterized by shared genetic influences on depression, anxiety and PTSD. However, bipolar disorder, OCD and anorexia nervosa were influenced by a genetic thought problems factor, rather than by internalizing. Lee et al[197] found that OCD and anorexia nervosa were influenced by a separate genetic factor from depression, whereas bipolar disorder had a uniquely strong association with schizophrenia (r_g=0.70). Finally, Levey et al[199] identified a genetic internalizing factor, which captured shared genetic influences on depression, NA/N, PTSD and anxiety.

Overall, genomic SEM supports a narrow internalizing factor that captures shared genetic influences on distress and fear disorders. Anorexia nervosa and OCD share a separate genetic factor in these studies, in line with the moderate genetic correlation between these conditions (r_g=0.45)[200]. Furthermore, the genetic vulnerability to bipolar disorder appears to align more closely with thought disorder than with internalizing. However, the high genetic overlap between schizophrenia and bipolar disorder is more specific to bipolar disorder I than bipolar disorder II (r_g=0.71 vs. 0.51), whereas depression is more closely correlated with bipolar disorder II than bipolar disorder I (r_g=0.69 vs. 0.30)[201]. Similarly, bipolar disorder cases with psychosis have higher genetic risk for schizophrenia but lower risk for anhedonia, whereas bipolar cases with a suicide attempt have elevated genetic risk for depression and anhedonia[202].

Molecular genetic studies also provide evidence for a genetic distinction between distress and fear factors. Depression and generalized anxiety show a substantial genetic overlap (r_g=0.80),

but are partly genetically distinct from fear disorders, such as specific phobia and panic (r_g=0.34 and 0.63, respectively)[203]. Moreover, depression and anxiety were influenced by two distinct but genetically correlated factors (r_g=0.80), while NA/N items were partitioned between them[204]. Likewise, the molecular genetic architecture of NA/N consists of two genetically correlated factors, corresponding to distress and fear[142,205,206].

As additional GWAS summary statistics become available, more fine-grained models of internalizing can be tested. Furthermore, although there is no GWAS of somatoform spectrum disorders, moderate genetic correlations between chronic pain and depression, anxiety and NA/N (r_g=0.40-0.59) suggest that there may be considerable genetic overlap between the internalizing and somatoform spectra, that is captured by the emotional dysfunction superspectrum[207,208]. Finally, genetic correlations can be affected by the heterogeneous psychiatric diagnoses used in GWAS. Homogeneous symptom dimensions can address this heterogeneity and enhance gene discovery[209-211].

Environmental risk factors

Environmental variation shapes the development of all forms of emotional disorder[212]. A vast literature attests to this fact, but studies focus primarily on a single diagnosis or a small cluster of disorders. Only recently has research begun to investigate environmental exposures in relation to quantitative dimensions that cut across traditional diagnostic boundaries.

Few risks are as potent as childhood maltreatment. Abuse and neglect confer long-lasting vulnerability to all types of emotional and somatic complaints. Keyes et al[49] created a model to explain this non-specificity in the US National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). They showed that maltreatment events predicted individual differences on an internalizing spectrum that represented the commonality among interview-based anxiety and depression diagnoses. Their model also allowed for the possibility of pathways from maltreatment to the unique part of each diagnosis that was independent of all other internalizing conditions. These diagnosis-specific effects were all comparatively weak, however, leading the authors to conclude that the relationship between maltreatment and emotional complaints could be represented solely by maltreatment's link with the internalizing spectrum. Several prospective studies have corroborated this finding[8,213-216].

Adolescent stressors are often proximal triggers for first onsets of diagnosable emotional problems. Social disruption, such as peer victimization, is particularly salient during this period. Forbes et al[217] hypothesized that victimization's influence on the internalizing spectrum could explain its far-reaching effects. They found that victimization experiences, such as verbal abuse and relational aggression, were robustly linked to an array of self-rated emotional problems. They observed that these various effects were almost entirely mediated by an overarching internalizing factor. Other developmental research has documented the same pattern across a number of different challenges, including romantic problems, family discord, and financial difficulty[218]. Moreover, it appears that differences on the internalizing spectrum predict the occurrence of *future* significant stressors, setting into motion a vicious cycle of stress exposure and worsening emotional problems[1,219].

Other aspects of the social milieu have demonstrated transdiagnostic effects on emotional complaints. For instance, racial discrimination is linked with a propensity to internalizing distress, but it is not specifically related to any particular type of emotional pathology[220]. Similarly, marital dissatisfaction is closely tied to a quantitative internalizing dimension rather than to individual forms of psychopathology[85]. Other parts of the social environment also tend to have stronger effects on internalizing than on its constituent diagnostic categories[1].

It is not groundbreaking to find that environmental stressors are pathogenic. The key insight is that they seem to convey risk for such a broad range of emotional conditions because they operate primarily at the level of the higher-order internalizing spectrum, as opposed to specific manifestations thereof. This will not necessarily be the case across all environmental exposures, emotional phenotypes, or populations, but it is a robust trend thus far.

More research is needed to extend this paradigm to the full range of emotional dysfunction phenotypes. It is particularly important to investigate environmental variation relevant to the somatoform spectrum. Environmental events are implicated in the onset of somatoform disorders[221], but there is little research on this topic from a quantitative modeling perspective. Twin, adoption and quasi-experimental designs also are needed to explicate the causal nature of observed effects.

Cognitive and affective difficulties

The internalizing spectrum is associated with cognitive difficulties that can be broadly characterized as cognitive inflexibility and behavioral disinhibition. In addition, affective difficulties – such as hyposensitivity to reward and/or hypersensitivity to punishment – appear intertwined with impaired inhibition, attentional control and decision-making, and contribute to most internalizing disorders. In general, these cognitive-affective problems likely reflect a compromised ability to inhibit intrusive and perseverative thoughts and emotions governing responses such as reward seeking and/or aversion to punishment, thereby contributing to a pattern of aberrant emotional responses and maladaptive decision-making.

Cognitive and affective difficulties are common in disorders within the distress subfactor. MDD has been linked to cognitive difficulties encompassing aspects of psychomotor speed, attention, verbal fluency, visual learning and memory, and executive functioning[222-226]. These problems become more severe as the disorder progresses. Similarly, PTSD is associated with temporal changes in severity of problems in attention, memory and executive functioning[227,228]. PTSD is also linked with attentional bias towards trauma-related stimuli[229], general inhibitory control deficits[230], and attenuated reward processing[231]. These problems provide some evidence of reduced cognitive flexibility and be-

havioral disinhibition.

Cognitive and affective difficulties – which suggest cognitive inflexibility and behavioral disinhibition – are observed in all disorders within the fear subfactor, albeit to varying degrees of severity. There is evidence of mild executive functioning and memory problems in panic disorder, social phobia, specific phobias and GAD[232-236], whereas difficulties found in OCD tend to be more severe[236]. OCD is strongly associated with reduced cognitive flexibility, as well as difficulties in other cognitive domains[237-239]. Unsurprisingly, anxiety-related disorders are linked to difficulties in social cognition[239,240].

Disorders within the eating pathology subfactor are characterized by difficulties with attentional inhibition, biased attention to disorder-related stimuli, and attentional set-shifting; these are common indicators of reduced cognitive and behavioral flexibility[241-243] that likely underlie problems with emotional regulation and decision-making. There is additional evidence that individuals with eating disorders have compromised visuospatial ability, verbal functioning, learning and memory[244]. Other evidence suggests that eating disorders are associated with difficulties in integrative information processing, a cognitive perceptual-processing style termed weak central coherence[245].

There are limited data related to objective measures of cognitive functioning in individuals with sexual disorders. However, there is evidence of perseverative cognitive schemas[246,247], which are likely attributable to cognitive inflexibility and/or behavioral disinhibition.

Children, adolescents and college students with general internalizing symptoms show sluggish cognitive tempo[248,249], which is linked with associated decrements in processing speed[249]. Internalizing is also associated with decreased cognitive flexibility in adolescents[250], which is consistent with difficulties in executive functions across various internalizing subfactors.

Bipolar disorders I and II are associated with cognitive problems in attention, memory and executive functions[224,251-253]. Common with the other internalizing subfactors, there is evidence that bipolar disorder II is associated with reduced inhibitory control[254]. In contrast to most internalizing conditions, however, bipolar disorder is associated with *hypersensitivity* to rewards[254,255].

Finally, few studies have explored cognitive difficulties in somatoform disorders. The available evidence suggests that the somatoform spectrum is associated with difficulties in attention and memory, and reduced attentional control in relation to threatening stimuli[256,257]. The limited available data suggest that this factor is linked with behavioral disinhibition, but more research is needed.

Neural substrates: neuroimaging

Across the internalizing spectrum, the neuroimaging literature varies by subfactor and modality to include magnetic resonance imaging (MRI) sequences of functionality (i.e., blood oxygen level-dependent activation, connectivity) and structure (i.e., volumetric, diffusion tensor imaging), as well as studies using nuclear imaging to reveal regional metabolic states – i.e., positron emission tomography (PET) and single photon emission computed tomography (SPECT).

This evidence indicates a range of functional disruptions (i.e., diminished or accentuated activity and connectivity) or aberrations (i.e., decreased white matter integrity and reduced volume) in neuroanatomical regions and pathways. The severity of these disruptions and aberrations is influenced by issues involving methodology, disorder comorbidity, illness phase/severity, genetics, pharmacology, and pathophysiology. Nevertheless, most studies show mild-to-moderate differences in comparison to controls or other clinical groups. Overall, the findings highlight the shared underlying neurobiology of the internalizing spectrum, which commonly includes fronto-striatal and fronto-limbic circuitry implicated in compromised self-regulation of behavior and processing of emotions in response to salient reward or punishment.

The literature on the distress subfactor is well established. Borderline personality disorder and PTSD share common neuropathological pathways, namely those included in cognitive-limbic circuitry[258]. MDD is associated with reduced volume of both cortical and limbic regions[259]. PTSD and MDD show altered activation in regions associated with cognition and emotion[260,261]. PTSD is associated with alterations in white matter tracts involved in executive functions, context learning and memory, salience processing, and emotional control[262]. MDD and PTSD both show reduced brain volume of specific regions, with PTSD showing greater reductions overall[263]. In MDD, there are also significant reductions in white matter tracts involved in cognition, memory and emotion[264]. For GAD, there is functional and structural evidence of alterations in frontal-limbic neurocircuitry[265]. Overall, the findings suggest compromised fronto-limbic-striatal circuitry in this subfactor.

There is substantial evidence of compromised functioning and structural differences within the fear subfactor. Most data come from studies of OCD and social anxiety, followed by phobias, with less evidence for other fear disorders. Overall, there appears to be consistent hyperactivation of regions implicated in cognitive-emotional responses to threat[266-272]. Alterations in connectivity are shared between fear disorders (e.g., panic disorder and social phobia); although these might include disruptions (e.g., hypoconnectivity) within various interdependent neural networks, most often there are alterations in fronto-striatal connectivity[273,274]. Alterations within the sensorimotor network are observed primarily in panic disorder. The limited structural evidence shows compromised white matter integrity, and differences in cortical and subcortical volume[269,275].

The eating pathology subfactor is characterized by compromised self-regulation and aberrant reward processing[276-279]. Studies show compromised connectivity and abnormal regional activation in response to reward[278]. There is also evidence of underlying neuroendocrine dysfunction[280]. In terms of structural evidence, there are inconsistencies in findings from volumetric studies and a small but growing literature indicating compromised white matter tracts[281-283]. Overall, findings provide

evidence to implicate disrupted functioning of fronto-striatal circuits involved in cognitive-emotional control.

There is little neuroimaging research related to sexual problems. However, the handful of papers are consistent in showing altered neural activity, namely hypoactivation of areas associated with cognition, motivation and autonomic arousal, and increased activation of the self-referential network[284,285]. Few studies have investigated structural differences or white matter integrity in this subfactor.

The mania subfactor is interstitial between internalizing and thought disorder, sharing a number of neural abnormalities with psychotic disorders[11]. However, in line with the theme observed in internalizing, bipolar disorder is associated with disrupted fronto-limbic circuitry as evidenced by altered white matter tracts and abnormal regional activation[286-289].

There is evidence of structural and functional aberrations in the somatoform spectrum. Due to methodological confounds, the literature is not as strong as in areas such as distress and fear. Nevertheless, the findings suggest disruptions or alterations in the fronto-striatal-limbic network[290].

Neural substrates: neurophysiology

Neurophysiological measures provide more direct indicators of neural activity that have greater temporal sensitivity. Internalizing conditions most frequently have been examined using electroencephalography (EEG), including both spectral power and event-related potentials (ERPs), which index a number of different cognitive, emotional and motivational processes.

Frontal EEG asymmetry is a relative difference in alpha power between the right and left frontal regions[291,292]. Alpha activity has been shown to index inhibition of cortical activity, and lower frontal EEG asymmetry scores (right alpha minus left alpha) are posited to reflect relatively less left than right cortical activity. Frontal EEG asymmetry has primarily been interpreted via an approach-withdrawal model[293], such that less relative left cortical activity is thought to reflect reduced approach motivation and increased withdrawal motivation.

The distress subfactor has demonstrated the most substantial association with frontal EEG asymmetry[294], although the evidence is inconsistent[295]. MDD and depression symptoms have been associated with a lower relative left frontal EEG asymmetry, both at rest and during emotional and motivational tasks[296-302]. Panic disorder[303] and OCD[304] have also been associated with a lower relative left frontal EEG asymmetry. In contrast, onset of bipolar disorder is predicted by *greater* relative left frontal EEG asymmetry[305].

The reward positivity (RewP), also known as the feedback negativity, is an ERP component reflecting reinforcement learning and reward system activation[306]. The RewP has demonstrated the most consistent association with the distress subfactor[307,308]. MDD and depression symptoms have been associated with a more blunted RewP in both adolescents and adults[309-316]. GAD symptoms have also been associated with a more blunted RewP [317]. The RewP has been associated with risk for, and family history of, MDD[318,319], and has been shown to predict major depressive episodes, first-onset depressive disorder, and greater depression symptoms prospectively[320,321].

The error-related negativity (ERN) is an ERP component that occurs in response to an error of commission and is posited to reflect the increased need for cognitive control and threat sensitivity[322]. An enhanced ERN has been associated with both fear and distress subfactors[323]. OCD, GAD and social anxiety all have been characterized by an enhanced ERN[324-330]. The ERN has been associated with risk for, and family history of, OCD[325,331,332], and has been shown to predict the development of first-onset anxiety disorders and GAD prospectively[333,334]. Within the somatoform spectrum, initial evidence suggests that health anxiety is associated with an enhanced ERN[335].

The P3 is a widely studied ERP component that is posited to index attentional allocation. Distress, eating and somatoform disorders all have been associated with a reduced P3[336-341]. These findings suggest that P3 alterations may be shared across the internalizing and somatoform spectra. Because P3 reductions have also been widely reported in psychosis and externalizing psychopathology[11,12], they may simply represent a marker of general psychopathology[342]. Enhanced P3, however, has also been associated with the internalizing spectrum, especially with its fear and eating pathology subfactors[343-346].

The late positive potential (LPP) is a later ERP component reflecting elaborative and sustained attention toward motivationally salient stimuli. The distress subfactor has been associated with a *reduced* LPP to emotional stimuli[347-351], whereas the fear subfactor has been associated with an *enhanced* LPP to aversive and unpleasant stimuli[349,352-355].

Other biomarkers

Disorders within the internalizing and somatoform spectra share several peripheral biomarkers related to stress reactivity. First, brain-derived neurotrophic factor (BDNF) assessed in blood serum and plasma indexes neuronal survival, synaptic signaling, and synaptic consolidation. Meta-analyses support reduced expression of BDNF in depression, bipolar disorder, suicide behavior, and eating pathology[356-361].

Second, cortisol productivity is a biomarker of hypothalamic-pituitary-adrenal axis function. Increased cortisol levels have been associated with distress[362-365], fear[233,366], and somatoform [367] conditions. Blunted cortisol, however, has also been reported[368,369], especially in PTSD[370]. Mixed findings exist for eating pathology[371,372] and may be explained by the heterogeneity in sample composition and symptom severity.

Third, elevated levels of pro-inflammatory markers in peripheral tissues are evident in emotional dysfunction disorders. Meta-analyses found elevated levels of C-reactive protein, interleukin (IL)-6, and tumor necrosis factor (TNF)-α in depression[373-376]; IL-6, IL-1β, TNF-α and interferon (IFN)-γ in PTSD[377,378]; IL-6 and TNF-α in bipolar disorder[373]; and IL-6 and TNF-α in anorexia nervosa[379]. However, there were no significant associations with bulimia nervosa[379]. Although it transcends diagnostic bounda-

ries, inflammation might nonetheless be attributable to specific symptoms such as sleep problems, appetite changes, and fatigue[380,381].

Finally, the gut-brain-microbiota axis is closely linked to the stress response, and a differential abundance of gut bacterial groups has been identified in depressive, anxiety, PTSD, bipolar, eating and pain-related psychopathology[382,383]. Some bacteria have been implicated across multiple conditions. For example, there is a reduction in the abundance of *Faecalibacterium* in patients with MDD[384], bipolar disorder[385], GAD[386], and irritable bowel syndrome[387].

Overall, peripheral biomarker studies indicate common biological signatures for disorders within the emotional dysfunction superspectrum. However, existing research is constrained by methodological limitations, including small sample sizes and a focus on a limited number of disorders. Moreover, the implicated biomarkers are also associated with other forms of psychopathology, such as schizophrenia[388]. Studies assessing multiple forms of psychopathology are needed to clarify the specificity versus non-specificity of these biological correlates.

Childhood temperament antecedents

Models of childhood temperament consistently highlight three dimensions that capture tendencies towards negative emotionality, approach-sociability (or surgency), and effortful control (or low impulsivity and disinhibition). These dimensions have close ties with basic traits of normative personality and maladaptive personality pathology[389-392].

Given that NA/N is the core of internalizing psychopathology, it is unsurprising that negative emotionality in childhood predicts subsequent internalizing[389,393]. This prospective association has been found not only for core internalizing dimensions, such as depression and anxiety symptoms, but also for eating pathology[394-396] and somatic symptoms[397]. However, other evidence suggests that youth negative emotionality is a non-specific risk for subsequent psychopathology broadly[8], particularly externalizing psychopathology[398,399].

Individual differences and behavior genetics research both suggest that low levels of approach-sociability (fearfulness, social withdrawal, behavioral avoidance) together with high levels of negative emotionality may be a combination of traits that differentiates internalizing from externalizing psychopathology[397,400,401]. Interestingly, this combination of high negative emotionality and low approach-sociability may predict anxiety, but not depression[402]. For example, a nationally representative cohort study of 4,983 Australian children followed from age 5 to 13 found that high negative emotionality in early childhood represented a broad risk for subsequent psychopathology, but low approach-sociability only uniquely predicted higher levels of anxiety[403]. This is consistent with the research finding that behavioral inhibition – a combination of negative emotionality and low approach – is a robust predictor of anxiety[404,405]. By contrast, high negative emotionality and *high* approach-sociability (and extraversion) were found to predict subsequent purging behaviors in adolescence[394], which is more consistent with patterns seen with externalizing disorders[403,406].

The third temperamental domain, (low) effortful control, appears to have an inconsistent association that is not specific to internalizing after controlling for concurrent levels of externalizing psychopathology[404]. Similarly, both high and low effortful control (persistence) in early childhood have been found to predict eating pathology in adolescence[407,408]. This domain seems to be a more specific and robust predictor of subsequent externalizing[12].

Illness course

Data from the US National Comorbidity Study Replication suggest that anxiety disorders generally have an earlier age of onset (50% by age 11) than depressive disorders (50% by age 32). However, this distinction is largely driven by disorders within the fear subfactor[409-411]. Age of onset for somatoform disorders appears to fall in between (50% by age 19[412]). Rates for both anxiety and depressive diagnoses decline in midlife (e.g., >55 years[413]).

Although traditionally discouraged as a diagnosis before adulthood, borderline personality disorder frequently emerges in late childhood or early adolescence[414]. Within eating disorders, anorexia nervosa appears to have a mean age of onset between 16 and 19 years, with bulimia nervosa slightly later between 17 and 25 years[415].

Internalizing and somatoform diagnoses follow an episodic, oftentimes chronic, course. Within a hierarchical framework, there are three primary ways of conceptualizing course: homotypic (i.e., course within a single condition), heterotypic (i.e., relations between different conditions over time), and latent liability (i.e., the course exhibited by a shared underlying factor). Psychiatric research traditionally has emphasized homotypic course. For example, using the NESARC dataset, which has two waves separated by approximately three years, Lahey et al[416] found moderate to strong homotypic continuity of six internalizing diagnoses (tetrachoric r = .41-.56). Bruce et al[410] showed that the probability of recovery was only moderate for GAD, social phobia, and panic disorder with agoraphobia, but high for MDD and panic disorder without agoraphobia; however, risk for recurrence was high for all disorders over a 12-year span. Shea and Yen[417] found that MDD showed high rates of both remission and recurrence over a two-year follow-up; in contrast, anxiety disorders had very low recovery rates, even after five years. Similar findings emerge in epidemiological samples, although more individuals appear to recover without recurrence[418].

Two studies of large clinical samples found high rates of remission (85-99%) for borderline personality disorder over the course of 10-16 years, with moderate rates of relapse (10-36%)[419,420]. A review suggested that anorexia and bulimia nervosa both show high remission (70-84%) over 10-16 years, with those who have not remitted often transitioning to an eating disorder not otherwise specified[421].

High rates of comorbidity raise questions of how this covariation manifests across time. Heterotypic continuity frames the

question of course in terms of whether a given form of psychopathology (e.g., MDD) at one point in time conduces to another (e.g., GAD) at a later point[422]. Lahey et al[416] found that heterotypic continuity was widespread within and across internalizing and externalizing diagnoses, although somewhat stronger within spectra. In fact, heterotypic continuity was comparable in magnitude to homotypic continuity, with significant heterotypic effects persisting after adjusting for all other diagnoses. Likewise, heterotypic developmental trajectories are the rule rather than the exception across childhood and adolescence, with childhood symptoms such as emotion dysregulation and irritability considered markers of a broad vulnerability for subsequent mental illness[423,424]. Relatedly, Moffitt et al[425] found that neither GAD nor MDD preferentially preceded the other, and ordering effects were symmetrical. Few studies have examined the stability of somatoform disorders, but four-year stability in early adulthood was high when considering heterotypic continuity[426].

Given this widespread heterotypic continuity, it becomes important to chart the course of the shared liability attributable to the higher-order spectra. In early adulthood (ages 18-25), longitudinal continuity among diagnoses was best accounted for by the stability of a general internalizing factor[427]. The same appears true in later adulthood, as latent internalizing factors were significantly correlated between age 41 and ages 56 (r=.51) and 61 (r=.43); these associations could largely be explained by genetic factors[428]. Relatedly, the substantial heterotypic continuity of depression and anxiety symptoms, and of different eating pathology symptoms, was largely attributable to stable, common genetic influences[173,429,430]. Finally, Wright et al[431] found that an interview-assessed, disorder-based internalizing factor strongly predicted a symptom-based internalizing factor (beta=.60) assessed via daily diary 1.4 years later. Overall, the evidence suggests that spectra represent the primary pathways of illness course, and constitute liabilities for the development of multiple conditions across the lifespan.

Treatment response

Given the high rates of comorbidity and the ubiquitously positive treatment response to cognitive behavior therapy (CBT) across various internalizing disorders[432-434], there has been a focus on testing treatments that were designed to be transdiagnostic (i.e., target multiple disorders). Meta-analyses of transdiagnostic theory-based CBT protocols for internalizing have demonstrated medium to large effect sizes for anxiety and depression, that were maintained at post-treatment follow-up[432-435]. There are particularly large effects for CBT in youth when parents are more involved in treatment[436].

Findings indicate no significant differences between transdiagnostic CBT and disorder-specific CBT protocols, which supports the efficacy of transdiagnostic CBT for internalizing[434,435]. Moreover, although there has been concern about including certain diagnoses (e.g., OCD and PTSD) in transdiagnostic CBT treatments, Norton et al[437] showed that transdiagnostic treatments for DSM-IV anxiety disorders were not associated with differential outcome by diagnosis.

Similar to transdiagnostic CBT, the unified protocol (UP) for the transdiagnostic treatment of emotional disorders was specifically designed to target co-occurring internalizing disorders[438,439]. Studies show that the UP is equivalent in effectiveness to gold-standard treatments designed to target single disorders[438,440]. The UP is much more efficient than single-disorder treatments, because clinicians only need to learn one protocol to treat internalizing disorders. Preliminary efficacy data show that, across diagnostic categories, the UP results in significant improvements in daily functioning, mood, depression, anxiety, and sexual functioning[441-444]. Treatment benefits from the UP were maintained at 6- to 12-month follow-up[443-445]. Transdiagnostic interventions are now being extended to flexible modular protocols in adults[446], mirroring efficacious modular transdiagnostic treatments across the internalizing spectrum in youth[447].

Interpersonal psychotherapy (IPT) is efficacious for treating certain internalizing disorders, such as depression and bulimia nervosa[448,449], although results were less pronounced and slower to emerge for the latter condition[449]. One review indicated that IPT was superior to CBT in treating depression[448]. Variants of IPT, including interpersonal social rhythm therapies (IPSRT), are beneficial as acute and maintenance treatments for both unipolar and bipolar depression[450-452], but have not been studied extensively in other forms of internalizing. Thus, there is support of IPT as a treatment for some, but not all, forms of internalizing, with the majority of research showing that it may be a useful treatment for distress and eating disorders, with limited efficacy for fear-based disorders, such as social phobia[453].

The limited available evidence indicates that treatments used for internalizing disorders (i.e., CBT and antidepressants) also are efficacious for somatic symptom disorders[221,454]. Although findings are mixed, CBT has been found to have lasting benefits for up to 12 months post-treatment[455-458].

Turning to pharmacological treatments, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are efficacious for the treatment of several internalizing disorders compared to placebo[459,460]; however, SSRIs are associated with an increased risk for sexual dysfunction[93]. Meta-analyses showed that atypical antipsychotics were significantly more efficacious for treating unipolar and bipolar depression and PTSD compared to placebo[461-464]. Another meta-analysis of off-label uses of antipsychotics found that quetiapine resulted in significant improvements in GAD symptoms, whereas risperidone significantly reduced OCD symptoms[465]. A large clinical trial found that olanzapine significantly increased weight gain in the treatment of anorexia nervosa compared to placebo[466]. However, atypical antipsychotics had limited benefits for improving quality of life in people with depression[467] and did not impact psychological symptoms in individuals with anorexia nervosa[466]. Overall, substantial data indicate that SSRIs and SNRIs are beneficial for treating most internalizing conditions, with accumulating evidence that atypical antipsychotics may be useful adjunctive medications. The available evidence for the ef-

ficacy of pharmacological treatments for somatoform disorders appears mixed and of low quality[468].

Summary of validity evidence

Table 3 summarizes the validity evidence reviewed in previous sections. It is noteworthy that virtually all associations are transdiagnostic in nature. That is, the studied variables are not simply related to a single form of psychopathology, but rather are associated with multiple conditions within the emotional dysfunction superspectrum (and, in many cases, to other forms of psychopathology as well). Studies have shown that multiple dimensions falling within the superspectrum share genetic diatheses, environmental risk factors (e.g., childhood maltreatment, financial difficulty, racial discrimination), cognitive and affective deficits (e.g., cognitive inflexibility, behavioral disinhibition), neural substrates (e.g., impaired fronto-striatal and fronto-limbic circuitry, blunted RewP, enhanced ERN) and other biomarkers (e.g., pro-inflammatory markers), as well as childhood temperamental antecedents (e.g., high negative emotionality, low surgency). Not surprisingly, therefore, dimensions within this spectrum respond to the same transdiagnostic treatments (including CBT and SSRIs) and are substantially related to one another both concurrently and prospectively.

These validity data are quite congruent with the structural evidence reviewed earlier. That is, many variables are related to both internalizing and somatoform conditions, and these shared factors can be captured by the emotional dysfunction superspectrum; other variables are more clearly linked to one spectrum than the other, thereby accounting for their emergence as distinct spectra at a lower level of the hierarchy. Similarly, some variables show relatively non-specific associations with all major forms of internalizing, which helps to account for its coherence as a structural dimension; in contrast, other variables show stronger links to some types of internalizing than to others, consistent with the emergence of distinct subfactors within internalizing.

Two caveats are important to mention. First, several validators were also linked to other spectra (e.g., the psychosis superspectrum also responds to antipsychotics, the externalizing superspectrum also shows high childhood maltreatment, and all three superspectra are positively associated with pro-inflammatory markers)[11,12], such that the specificity of these associations is uncertain. Second, some internalizing conditions show a distinct profile on certain validators, which underscores the value of the lower levels of the HiTOP hierarchy. Mania, in particular, is distinct with regard to genetic liability, affective deficits, and episodic course.

UTILITY EVIDENCE

The internalizing and somatoform spectra show greater utility than traditional diagnoses with respect to reliability, explanatory power, and clinical utility.

As discussed earlier, the reliability of emotional dysfunction diagnoses tends to be unimpressive. The DSM-5 field trials found that interrater reliability (kappa coefficient) ranged from .20 (GAD) and .28 (MDD) to .61 (complex somatic symptom disorder) and .67 (PTSD)[25]. In these field trials, patients used a 5-point scale to report key symptoms of depression, anxiety, sleep, suicide, and somatic distress. Dimensional assessment substantially improved reliability for individual symptoms, with retest correlations ranging from .64 to .78 (mean=.70); symptom composites were even more reliable[27]. This underscores a consistent pattern that dimensional descriptions of psychopathology are more reliable than categories. Of note, some studies – such as a field study of ICD-11 diagnoses[469] – reported higher interrater reliabilities for diagnoses, but they used less stringent designs that may inflate reliability estimates[23].

In longitudinal studies, latent internalizing spectra have shown high long-term stability in childhood (test-retest r=.85 over 3 years)[62], young adulthood (r=.69 over 3 years)[45], and middle adulthood (r=.74 over 9 years)[470]. Likewise, the distress and fear subfactors showed impressive stability over two months (r = .81 and .87, respectively)[80], one year (r = .85 and .89)[86], and three years (r = .60 and .64)[73]. Comparable data are not available for other conditions within the superspectrum. Overall, a meta-analysis estimated the reliability of internalizing dimensions to be .82, a substantial improvement over categorical diagnoses[22].

The ability to explain functional impairments, risk factors, outcomes and treatment response is an essential feature of diagnostic utility. A meta-analysis found substantially higher explanatory power for internalizing dimensions (mean correlation r=.51) than categories (mean r=.32) across multiple validators[22]. Several studies directly compared HiTOP-consistent and DSM descriptions of internalizing psychopathology, finding that HiTOP dimensions explained twice as much variance in functional impairment[471] and the probability of antidepressant prescription[472]. Also, compared to DSM diagnoses, HiTOP dimensions explained six times more variance in impairment related to eating pathology[88], and predicted two times more variance in clinical outcomes 6-12 months later[473]. Thus, the HiTOP characterization of internalizing problems can substantially increase clinical utility.

The clinical utility of a nosology encompasses additional considerations, such as facilitating case conceptualization, communication with professionals and consumers, treatment selection, and improvement of treatment outcomes[474,475]. Existing research is limited by reliance on practitioner ratings, global evaluation of a system rather than individual spectra or disorder classes, and primary focus on personality disorders. Nevertheless, recent research consistently indicated that practitioners give higher ratings to dimensional descriptions than categorical diagnoses on most utility indicators[476-479]. In the DSM-5 field trials, dimensional measures were rated positively by 80% of clinicians[480]. Nevertheless, it is important to investigate the clinical utility of the internalizing and somatoform spectra specifically, and to study objective criteria of clinical utility, such as measured improvement in treatment outcomes.

The clinical acceptability of HiTOP is unsurprising, as it is

Table 3 Validators of the internalizing and somatoform spectra

		Internalizing					
	Somatoform	**Overall**	**Distress**	**Fear**	**Sexual problems**	**Eating pathology**	***Mania***
Genetics							
Family/twin heritability	+++	+++	+++	+++		+++	++
Molecular genetics	+	++	++	++		+	+
Environment							
Childhood maltreatment		+++					
Adolescent stressors	+	+++					
Racial discrimination		+++					
Relationship satisfaction		+++					
Cognition							
Cognitive deficits	+	+++	+++	+++	++	+++	+++
Affective deficits	++	+++	+++	+++	++	+++	+
Neurobiology							
Structural	+	++	+++	+++		++	++
Functional							
Neuroimaging	+	+++	+++	+++	+	+++	++
Electrophysiology	+	++	+++	+++		+	+
Biomarkers							
Reduced BDNF expression	+	+++	++	+		++	++
Cortisol alterations	++	+++	++	++	+	++	++
Pro-inflammatory markers	++	+++	++	++	+	++	++
Gut-brain microbiota	++	+++	++	++		++	++
Antecedents/Course							
High negative affectivity	+	+++	+++	+++	+	+++	
Low approach-sociability		+++		++		–	
Low effortful control		+					
Age of onset	+		+++	+++		+++	+++
Chronicity/stability	+		+++	+++		+++	+++
Treatment							
Response to CBT	++	+++	+++	+++	+		
Response to UP		+++	++	++	+		
Response to IPT		++	++	+		+++	+
Response to SSRIs	+	+++	+++	+++	–	+++	
Response to SNRIs	+	++	++	++		++	
Response to atypical antipsychotics		++	++	++		+	+

+: some evidence for effect, ++: some replications, +++: repeatedly replicated finding, –: effect in the opposite direction, BDNF – brain-derived neurotrophic factor, CBT – cognitive behavior therapy, UP – unified protocol, IPT – interpersonal psychotherapy, SSRIs – selective serotonin reuptake inhibitors, SNRIs – serotonin-norepinephrine reuptake inhibitors. Subfactors with ambiguous or inconsistent structural placement (in this case, mania) are italicized.

grounded in an established practice of conceptualizing patients according to symptom and trait dimensions. The HiTOP advances this practice by providing a rigorous system of dimensions and validated tools to assess them. It also recognizes the need for categorical decisions (e.g., to treat or wait) in clinical practice[481]. Multiple ranges of scores (e.g., none, mild, moderate and severe psychopathology) have been identified to support clinical decisions. The HiTOP consortium is developing additional ranges for specific clinical questions (e.g., indication for suicide prevention) using strategies that were established in other fields of medicine

for optimal categorization of dimensional measures[482,483].

In this, the HiTOP builds on a strong foundation of research and practice. Dimensional measures of emotional dysfunction are among the most widely used instruments in psychiatry, including the Hamilton Rating Scale for Depression[484], the Beck Depression Inventory[485], the Beck Anxiety Inventory[486], the Patient Health Questionnaire[487], and the Columbia-Suicide Severity Rating Scale[488]. However, such measures were developed to assess specific clinical conditions and none covers the internalizing or somatoform spectra comprehensively.

MEASUREMENT

Several broad symptom measures have been created to assess multiple higher- and lower-order internalizing dimensions. The original and expanded forms of the Inventory of Depression and Anxiety Symptoms (IDAS and IDAS-II, respectively) contain self-report scales assessing symptoms of depression, anxiety, PTSD, OCD and mania[100,489]. The IDAS-II scales index the HiTOP-consistent factors of distress, obsessions/fear, and positive mood/mania, with high internal consistency and stability over short intervals[100]. The Interview for Mood and Anxiety Symptoms targets dimensions similar to the IDAS-II, but with an interview format to capture the strengths of clinician-based assessment[80,471,490]. These instruments can be supplemented with the self-rated[90] and clinician-rated[491] versions of the Eating Pathology Symptoms Inventory, which provide comprehensive assessment of eating disorder symptoms. Widely used measures of sexual functioning are problematic[492], indicating a need for better assessment.

Omnibus personality inventories have demonstrated strong overlap with symptom measures of internalizing[105,493]. The Personality Inventory for DSM-5 (PID-5)[494], the Schedule for Nonadaptive and Adaptive Personality[495], and the Dimensional Assessment of Personality Pathology - Basic Questionnaire[496] all contain personality trait facets (e.g., depressivity, emotional lability) that index the higher-order NA/N domain. The PID-5 specifically matches the DSM-5 alternative model of personality disorders as well as the proposed five ICD-11 trait domains[494,497,498]. The Minnesota Multiphasic Personality Inventory-2-Restructured form (MMPI-2-RF)[499] and the Personality Assessment Inventory (PAI)[500] both provide clinical measurement (with population representative norms) of the internalizing and somatoform spectra, with well-validated scales that capture the higher-order level (e.g., MMPI-2-RF emotional/internalizing dysfunction and somatic complaints) and much of the lower-order level (e.g., MMPI-2-RF: low positive emotions, stress/worry, anxiety, malaise, neurological complains; PAI: depression-cognitive, anxiety-physiological, somatic conversion)[2,501,502].

Evidence for a distinct somatoform spectrum[47,103,105] indicates the need to measure somatization symptoms in detail. A systematic review of self-report questionnaires for common somatic symptoms has identified a total of 40 measures, with the majority deemed unsuitable for future use[503]. The authors concluded, however, that the Patient Health Questionnaire-15[504] and the Symptom Checklist-90 Somatization Scale[505] were the most suitable scales, given their validity, internal consistency, content coverage, replicable structure, and short-term stability[503]. The Bodily Distress Scale (BDS)[108] is a more recent measure of the bodily distress syndrome[118,119], which encompasses a large range of somatoform facets. None of these measures cover health anxiety, however, which can be assessed using the Whiteley Index[506] or the more comprehensive Multidimensional Inventory of Hypochondriacal Traits[120].

RESEARCH IMPLICATIONS

The HiTOP model highlights the limitations of traditional case-control studies in which patients with a given disorder are compared to individuals without that disorder[11]. The key problem with this design is that cases will differ from controls on many variables other than the assessed disorder. In particular, these studies ignore the pervasive problem of diagnostic comorbidity[2]. In light of this comorbidity, it is unclear whether a reported finding actually is due to the target disorder *per se*, or instead is attributable to another comorbid condition or even non-specific features that are shared between them (e.g., the higher-order internalizing spectrum).

The HiTOP emphasizes the importance of assessing highly correlated "near neighbor" conditions that show particularly strong comorbidity. For example, Kessler et al[507] examined 12-month DSM-III-R diagnoses in two large national samples: the National Comorbidity Survey (NCS)[508] and the Midlife Development in the United States Survey (MIDUS)[509]. Of those diagnosed with GAD, 58.1% (NCS sample) and 69.7% (MIDUS sample) also had MDD. Thus, in a typical case-control study, many – perhaps most – patients with GAD also will meet criteria for MDD. Without also assessing MDD, it is impossible to know whether any observed findings are actually attributable to GAD.

However, the identification of broad spectra and superspectra in the HiTOP model indicates that the problem is much more pervasive than this, such that most forms of psychopathology co-occur beyond chance and are positively correlated with one another. For example, an analysis of NCS diagnoses indicated that 87.6% of those with agoraphobia, 83.4% of those with simple phobia, and 81.0% of those with social phobia met criteria for at least one other lifetime disorder; moreover, roughly half of these individuals (54.0%, 52.5%, and 48.0, respectively) met criteria for three or more additional disorders[510]. Of those who met criteria for agoraphobia, 46.5% also were diagnosed with social phobia, 45.9% had MDD, 45.6% had simple phobia, and 36.3% met criteria for substance abuse. As a general rule, those who are diagnosed with a given disorder are also likely to show elevated rates of many other forms of psychopathology[422,511].

Consequently, studies need to assess psychopathology broadly in order to produce interpretable results. For example, if one only assesses agoraphobia, it is unclear whether any observed findings are attributable to this disorder, another internalizing condition, or the broad internalizing factor that represents

shared features of these disorders. Furthermore, without assessing conditions that fall outside of internalizing, it is unclear whether findings are actually specific to this spectrum or are even more broadly associated with psychopathology.

Fortunately, the HiTOP provides a highly efficient framework for designing maximally informative studies. As a general principle, it is important to concentrate assessment on those regions of the hierarchy that are nearest to the condition of interest; other portions of the structure can be sampled more sparingly. To facilitate the development of a more comprehensive design, we recommend population-based sampling (perhaps oversampling those who are likely to report elevated levels of psychopathology) with very broad inclusion criteria. With regard to measurement, we encourage the use of the types of HiTOP-conformant instruments that were described earlier; homogeneous dimensional scales are more efficient, reliable, valid and informative than traditional categorical diagnoses.

CLINICAL IMPLICATIONS

The HiTOP facilitates a flexible approach to treatment. Its hierarchical structure models psychopathology dimensions at increasing levels of generality, ranging from narrow, homogeneous symptoms and traits to broad spectra and superspectra. Clinicians are free to focus on whatever level is most informative for case conceptualization and treatment. In this regard, it is noteworthy that the broader dimensions occupying the upper levels of the hierarchy are congruent with the increasing focus on transdiagnostic approaches to treatment, which were reviewed earlier[432-446]. Among these transdiagnostic treatments, the UP [438-445] is particularly relevant to the forms of psychopathology discussed in this paper. The UP was developed to be "applicable across anxiety and mood disorders, as well as other disorders in which anxiety and emotional dysregulation play a significant role, such as many somatoform and dissociative disorders"[512, p.89]; it is therefore designed to treat the full range of psychopathology subsumed within the emotional dysfunction superspectrum. The UP focuses particularly on helping patients to regulate negative emotions more effectively; in recent years, it has shifted to concentrate directly on reducing levels of NA/N[513,514].

Thus, the HiTOP provides some particularly efficient targets for transdiagnostic treatment. Nevertheless, some clinicians may be wary about working with dimensions. We therefore address two common concerns that have been raised with regard to dimensional measures in treatment. The first is that cutoffs are essential in practical clinical decision-making. It is true that scores often need to be dichotomized at some point to inform clinical decisions. It should be noted, however, that traditional diagnoses are not optimized for any particular clinical action[4,11]. Consequently, dimensional scores offer the distinct advantage that they can be cut in multiple ways to optimize different types of clinical decisions. For instance, Stasik-O'Brien et al[515] created three different cutoff scores for the IDAS scales: a screening cutoff (which is more lenient and maximizes sensitivity), a diagnostic cutoff (which is more conservative and maximizes specificity), and a balanced cutoff (which optimizes differentiation between those with and without a disorder).

A second argument is that dimensional models hinder the communication of clinically important information. However, quantitatively based dimensional schemes have been found to improve clinical communication, rather than hindering it[36,516]. This is because – all other things being equal – homogeneous dimensions are more easily interpretable than heterogeneous categories, and thus provide clearer, more trustworthy sources of information. If one is told that a patient has a high score on a narrow, specific symptom such as anhedonia, it is reasonably clear what that means. In contrast, if one is informed that a patient has been diagnosed with PTSD, it is much less clear what this means, given the marked heterogeneity of this disorder.

FUTURE DIRECTIONS

The HiTOP requires further development in several ways. First, the structure is currently incomplete. Some important forms of psychopathology (e.g., autism, neurocognitive disorders) are currently not included in the model due to insufficient evidence. More generally, the DSM-5 includes 19 diagnostic classes. At present, the HiTOP incorporates eight of them fully, six only in part (i.e., modeling some, but not all, conditions within the class), and five not at all[517].

Second, the placement of certain conditions needs to be clarified. For example, mania is interstitial and shows important connections to both internalizing and thought disorder. As noted earlier, it seems likely that specific symptom dimensions within mania (e.g., emotional lability, euphoric activation) fall in different parts of the HiTOP hierarchy. Consequently, these specific dimensions should be modeled in future structural work.

Third, future research should examine the emotional dysfunction superspectrum itself. The existence of this superspectrum remains provisional and is based on limited evidence. Furthermore, as discussed previously, some studies have found that somatoform symptomatology can be subsumed within internalizing[2]. It will be, therefore, important for future research to explicate the nature of the links between internalizing and somatoform pathology.

In addition, the HiTOP largely reflects associations between different forms of psychopathology that were assessed at the same point in time. As such, it essentially represents a static model of concurrent associations. Additional longitudinal research is needed to determine how different forms of psychopathology relate to each other dynamically over time. These dynamic relations are likely complex. For instance, early work suggested that anxiety symptoms and disorders were much more likely to precede depressive symptoms and disorders than vice versa[5,518]. However, a more recent meta-analysis found that "depressive disorders may be prodromes for social and specific phobia, whereas other anxiety and depressive disorders are bidirectional risk factors for one another"[519, p.1155].

Finally, as shown in Tables 1 and 2, the HiTOP model was created using data collected from different age groups and from a large number of countries. Nevertheless, the generalizability of this structure is limited. It will be important to test the generalizability of the hierarchical structure across a broader range of countries and age groups.

CONCLUSIONS

The HiTOP offers a dimensional, hierarchical conceptualization of psychopathology. It addresses problems of heterogeneity, comorbidity, poor coverage, and unreliability, thereby providing more valid and informative clinical descriptions than traditional nosological systems. It has been extensively validated and already demonstrates considerable utility.

Validated measures are currently available to assess the dimensions falling within the internalizing and somatoform spectra. Although further research is needed, the model is ready for use by scientists and clinicians.

APPENDIX

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REFERENCES

1. Conway CC, Forbes MK, Forbush KT et al. A Hierarchical Taxonomy of Psychopathology can transform mental health research. Perspect Psychol Sci 2019;14:419-36.
2. Kotov R, Krueger RF, Watson D et al. The Hierarchical Taxonomy of Psychopathology (HiTOP): a dimensional alternative to traditional nosologies. J Abnorm Psychol 2017;126:454-77.
3. Kotov R, Krueger RF, Watson D. A paradigm shift in psychiatric classification: the Hierarchical Taxonomy Of Psychopathology (HiTOP). World Psychiatry 2018;17:24-5.
4. Krueger RF, Kotov R, Watson D et al. Progress in achieving quantitative classification of psychopathology. World Psychiatry 2018;17:282-93.
5. Mineka S, Watson D, Clark LA. Comorbidity of anxiety and unipolar mood disorders. Annu Rev Psychol 1998;49:377-512.
6. Watson D. Rethinking the mood and anxiety disorders: a quantitative hierarchical model for DSM-V. J Abnorm Psychol 2005;114:522-36.
7. Watson D. Differentiating the mood and anxiety disorders: a quadripartite model. Annu Rev Clin Psychol 2009;5:221-47.
8. Caspi A, Houts RM, Belsky DW et al. The p factor: one general psychopathology factor in the structure of psychiatric disorders? Clin Psychol Sci 2014;2:119-37.
9. Lahey BB, Applegate B, Hakes JK et al. Is there a general factor of prevalent psychopathology during adulthood? J Abnorm Psychol 2012;121:971-7.
10. Lahey BB, Moore TM, Kaczkurkin AN et al. Hierarchical models of psychopathology: empirical support, implications, and remaining issues. World Psychiatry 2021;20:57-63.
11. Kotov R, Jonas KG, Carpenter WT et al. Validity and ultility of Hierarchical Taxonomy of Psychopathology (HiTOP): I. Psychosis superspectrum. World Psychiatry 2020;19:151-72.
12. Krueger RF, Hobbs KA, Conway CC et al. Validity and utility of the Hierarchical Taxonomy of Psychopathology (HiTOP): II. Externalizing superspectrum. World Psychiatry 2021;20:171-93.
13. Carragher N, Krueger RF, Eaton NR et al. ADHD and the externalizing spectrum: direct comparison of categorical, continuous, and hybrid models of liability in a nationally representative sample. Soc Psychiatry Psychiatr Epidemiol 2014;49:1307-17.
14. Clark LA, Watson D, Reynolds S. Diagnosis and classification of psychopathology: challenges to the current system and future directions. Annu Rev Psychol 1995;46:121-53.
15. Haslam N, Holland E, Kuppens P. Categories versus dimensions in personality and psychopathology: a quantitative review of taxometric research. Psychol Med 2012;42:903-20.
16. Haslam N, McGrath MJ, Vichtbauer W et al. Dimensions over categories: a meta-analysis of taxometric research. Psychol Med 2020;50:1418-32.
17. Markon KE, Krueger RF. Categorical and continuous models of liability to externalizing disorders: a direct comparison in NESARC. Arch Gen Psychiatry 2005;62:1352-9.
18. Walton KE, Ormel J, Krueger RF. The dimensional nature of externalizing behaviors in adolescence: evidence from a direct comparison of categorical, dimensional, and hybrid models. J Abnorm Child Psychol 2011;39:553-61.
19. Widiger TA, Samuel DB. Diagnostic categories or dimensions? A question for the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition. J Abnorm Psychol 2005;114:494-504.
20. Cohen J. The cost of dichotomization. Appl Psychol Meas 1983;7:249-53.
21. MacCallum RC, Zhang S, Preacher KJ. On the practice of dichotomization of quantitative variables. Psychol Methods 2002;7:19-40.
22. Markon KE, Chmielewski M, Miller CJ. The reliability and validity of discrete and continuous measures of psychopathology: a quantitative review. Psychol Bull 2011;137:856-79.
23. Chmielewski M, Clark LA, Bagby RM et al. Method matters: understanding diagnostic reliability in DSM-IV and DSM-5. J Abnorm Psychol 2015;124:764-9.
24. Markon KE. Epistemological pluralism and scientific development: an argument against authoritative nosologies. J Pers Disord 2013;27:554-59.
25. Regier DA, Narrow WE, Clarke DE et al. DSM-5 field trials in the United States and Canada, Part II: Test-retest reliability of selected categorical diagnoses. Am J Psychiatry 2013;170:59-70.
26. Chmielewski M, Ruggero CJ, Kotov R et al. Comparing the dependability and associations with functioning of the DSM-5 Section III trait model of personality pathology and the DSM-5 Section II personality disorder model. Personal Disord 2017;8:228-36.
27. Narrow WE, Clarke DE, Kuramoto SJ et al. DSM-5 field trials in the United States and Canada, Part III: Development and reliability testing of a cross-cutting symptom assessment for DSM-5. Am J Psychiatry 2013;170:71-82.
28. Samuel DB. A review of the agreement between clinicians' personality disorder diagnoses and those from other methods and sources. Clin Psychol Sci Pract 2015;22:1-19.
29. Shea MT, Stout R, Gunderson J et al. Short-term diagnostic stability of schizotypal, borderline, avoidant, and obsessive-compulsive personality disorders. Am J Psychiatry 2002;159:2036-41.
30. Watson D. Investigating the construct validity of the dissociative taxon: stability analyses of normal and pathological dissociation. J Abnorm Psychol 2003;112:298-305.
31. Watson D. Subtypes, specifiers, epicycles, and eccentrics: toward a more parsimonious taxonomy of psychopathology. Clin Psychol Sci Pract 2003; 10:233-8.
32. Zimmerman M, Ellison W, Young D et al. How many different ways do patients meet the diagnostic criteria for major depressive disorder? Compr Psychiatry 2015;56:29-34.
33. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed. Washington: American Psychiatric Publishing, 2013.
34. Fried EI, Nesse RM. Depression is not a consistent syndrome: an investigation of unique symptom patterns in the STAR*D study. J Affect Disord 2015;172:96-102.
35. Galatzer-Levy IR, Bryant RA. 636,120 ways to have posttraumatic stress disorder. Perspect Psychol Sci 2013;8:651-62.

36. Watson D, Ellickson-Larew S, Stanton K et al. Personality provides a general structural framework for psychopathology: commentary on "Translational applications of personality science for the conceptualization and treatment of psychopathology". Clin Psychol Sci Pract 2016;23:309-13.
37. Andrews G. Slade T, Issakidis C. Deconstructing current comorbidity: data from the Australian National Survey of Mental Health and Well-Being. Br J Psychiatry 2002;181:306-14.
38. Bijl RV, Ravelli A, van Zessen G. Prevalence of psychiatric disorders in the general population: results of the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Soc Psychiatry Psychiatr Epidemiol 1998;33:587-95.
39. Brown TA, Campbell LA, Lehman CL et al. Current and lifetime comorbidity of the DSM-IV anxiety and mood disorders in a large clinical sample. J Abnorm Psychol 2001;110:585-99.
40. Grant BF, Stinson FS, Dawson DA et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders. Arch Gen Psychiatry 2004;61:807-16.
41. Kessler RC, Chiu WT, Demler O et al. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Survey Replication. Arch Gen Psychiatry 2005;62:617-27.
42. Ormel J, Raven D, van Oort F et al. Mental health in Dutch adolescents: a TRAILS report on prevalence, severity, age of onset, continuity and co-morbidity of DSM disorders. Psychol Med 2015;45:345-60.
43. Teesson M, Slade T, Mills K. Comorbidity in Australia: findings of the 2007 National Survey of Mental Health and Wellbeing. Aust N Z J Psychiatry 2009;43:606-14.
44. Clark LA, Watson D. Distress and fear disorders: an alternative empirically based taxonomy of the 'mood' and 'anxiety' disorders. Br J Psychiatry 2006;189:481-3.
45. Krueger RF, Caspi A, Moffitt TE et al. The structure and stability of common mental disorders (DSM-III-R): a longitudinal-epidemiological study. J Abnorm Psychol 1998;107:216-27.
46. Forbes MK, Kotov R, Ruggero CJ et al. Delineating the joint hierarchical structure of clinical and personality disorders in an outpatient psychiatric sample. Compr Psychiatry 2017;79:19-30.
47. Kotov R, Ruggero CJ, Krueger RF et al. New dimensions in the quantitative classification of mental illness. Arch Gen Psychiatry 2011;68:1003-11.
48. Levin-Aspenson HF, Khoo S, Kotelnikova Y. Hierarchical taxonomy of psychopathology across development: associations with personality. J Res Pers 2019;81:72-8.
49. Keyes KM, Eaton NR, Krueger RF et al. Childhood maltreatment and the structure of common psychiatric disorders. Br J Psychiatry 2012;200:107-15.
50. Kim H, Eaton NR. The hierarchical structure of common mental disorders: connecting multiple levels of comorbidity, bifactor models, and predictive validity. J Abnorm Psychol 2015;124:1064-78.
51. Kendler KS, Aggen SH, Knudsen GP et al. The structure of genetic and environmental risk factors for syndromal and subsyndromal common DSM-IV Axis I and all Axis II disorders. Am J Psychiatry 2011;168:29-39.
52. Røysamb E, Tambs K, Ørstavik RE et al. The joint structure of DSM-IV Axis I and Axis II disorders. J Abnorm Psychol 2011;120:198-209.
53. Kessler RC, Ormel J, Petukhova M et al. Development of lifetime comorbidity in the World Health Organization World Mental Health Surveys. Arch Gen Psychiatry 2011;68:90-100.
54. Conway CC, Brown TA. Evaluating dimensional models of psychopathology in outpatients diagnosed with emotional disorders: a cautionary tale. Depress Anxiety 2018;35:898-902.
55. Conway CC, Mansolf M, Reise SP. Ecological validity of a quantitative classification system for mental illness in treatment-seeking adults. Psychol Assess 2019;31:730-40.
56. Conway CC, Starr LR, Espejo EP et al. Stress responsivity and the structure of common mental disorders: transdiagnostic internalizing and externalizing dimensions are associated with contrasting stress appraisal biases. J Abnorm Psychol 2016;125:1079-89.
57. Farmer RF, Seeley JR, Kosty DB et al. Hierarchical organization of axis I psychiatric disorder comorbidity through age 30. Compr Psychiatry 2013;54:523-32.
58. Girard JM, Wright AG, Beeney JE et al. Interpersonal problems across levels of the psychopathology hierarchy. Compr Psychiatry 2017;79:53-69.
59. King SM, Saunders GR, Elkins IJ et al. Where do gambling problems fit in the structure of psychopathology during emerging adulthood? Int Gambl Stud 2020;20:1-13.
60. Kotov R, Chang S-W, Fochtmann LJ et al. Schizophrenia in the internalizing-externalizing framework: a third dimension? Schizophr Bull 2011;37:1168-78.
61. Martel MM, Pan PM, Hoffman MS et al. A general psychopathology factor (p factor) in children: structural model analysis and external validation through familial risk and child global executive function. J Abnorm Psychol 2017;126:137-48.
62. Olino TM, Bufferd SJ, Dougherty LR et al. The development of latent dimensions of psychopathology across early childhood: stability of dimensions and moderators of change. J Abnorm Child Psychol 2018;46:1373-83.
63. Schaefer JD, Moffitt TE, Arsenault L et al. Adolescent victimization and early-adult psychopathology: approaching causal inference using a longitudinal twin study to rule out noncausal explanations. Clin Psychol Sci 2018;6:352-71.
64. Scott LN, Victor SE, Kaufman EA et al. Affective dynamics across internalizing and externalizing dimensions of psychopathology. Clin Psychol Sci 2020;8:412-27.
65. Verona E, Sachs-Ericsson N, Joiner TE Jr. Suicide attempts associated with externalizing psychopathology in an epidemiological sample. Am J Psychiatry 2004;161:444-51.
66. Verona E, Javdani S, Sprague J. Comparing factor structures of adolescent psychopathology. Psychol Assess 2011;23:545-51.
67. Wright AG, Simms LJ. A metastructural model of mental disorders and pathological personality traits. Psychol Med 2015;45:2309-19.
68. Beesdo-Baum K, Höfler M, Gloster AT et al. The structure of common mental disorders: a replication study in a community sample of adolescents and young adults. Int J Methods Psychiatr Res 2009;18:204-20.
69. Wittchen HU, Beesdo-Baum K, Gloster AT et al. The structure of mental disorders re-examined: is it developmentally stable and robust against additions? Int J Methods Psychiatr Res 2009;18:189-203.
70. Cox BJ, Clara IP, Enns MW. Posttraumatic stress disorder and the structure of common mental disorders. Depress Anxiety 2002;15:168-71.
71. Krueger RF. The structure of common disorders. Arch Gen Psychiatry 1999; 56:921-6.
72. Eaton NR, Krueger RF, Keyes KM et al. Borderline personality disorder comorbidity: relationship to the internalizing-externalizing structure of common mental disorders. Psychol Med 2011;41:1041-50.
73. Eaton NR, Krueger RF, Keyes KM et al. The structure and predictive validity of the internalizing disorders. J Abnorm Psychol 2013;122:86-92.
74. Keyes KM, Eaton NR, Krueger RF et al. Thought disorder in the meta-structure of psychopathology. Psychol Med 2013;43:1673-83.
75. de Jonge P, Wardenaar KJ, Lim CC et al. The cross-national structure of mental disorders: results from the World Mental Health Surveys. Psychol Med 2018;48:2073-84.
76. Blanco C, Wall MM, Jian-Ping H et al. J Am Acad Child Adolesc Psychiatry 2015;54:45-52.
77. Forbush KT, Watson D. The structure of common and uncommon mental disorders. Psychol Med 2013;43:97-108.
78. Forbush KT, South SC, Krueger RF et al. Locating eating pathology within an empirical diagnostic taxonomy: evidence from a community-based sample. J Abnorm Psychol 2010;119:282-92.
79. James LM, Taylor J. Revisiting the structure of mental disorders: borderline personality disorder and the internalizing/externalizing spectra. Br J Clin Psychol 2008;47:361-80.
80. Kotov R, Perlman G, Gámez W et al. The structure and short-term stability of the emotional disorders: a dimensional approach. Psychol Med 2015;45:1687-98.
81. Miller MW, Fogler JM, Wolf EJ et al. The internalizing and externalizing structure of psychiatric comorbidity in combat veterans. J Trauma Stress 2008;21:58-65.
82. Miller MW, Wolf EJ, Reardon A et al. Personality and the latent structure of PTSD comorbidity. J Anxiety Disord 2012;26:599-607.
83. Mitchell KS, Wolf EJ, Reardon AF et al. Association of eating disorder symptoms with internalizing and externalizing dimensions of psychopathology among men and women. Int J Eat Disord 2014;47:860-9.
84. Slade T, Watson D. The structure of common DSM-IV and ICD-10 mental disorders in the Australian general population. Psychol Med 2006;36:1593-600.
85. South SC, Krueger RF, Iacono WG. Understanding general and specific connections between psychopathology and marital distress: a model based approach. J Abnorm Psychol 2011;120:935-47.
86. Vollebergh WA, Iedema J, Bijl RV et al. The structure and stability of common mental disorders: the NEMESIS Study. Arch Gen Psychiatry 2001;58:597-603.
87. Wright AG, Krueger RF, Hobbs MJ et al. The structure of psychopathology: toward an expanded quantitative empirical model. J Abnorm Psychol

2013;122:281-94.
88. Forbush KT, Hagan KE, Kite BA et al. Understanding eating disorders within internalizing psychopathology: a novel transdiagnostic, hierarchical-dimensional model. Compr Psychiatry 2017;79:40-52.
89. Coniglio KA, Becker KR, Tabri N et al. Factorial integrity and validation of the Eating Pathology Symptoms Inventory (EPSI). Eat Behav 2018;31:1-7.
90. Forbush KT, Wildes JE, Pollack LO et al. Development and validation of the Eating Pathology Symptoms Inventory (EPSI). Psychol Assess 2013:25:859-78.
91. Forbush KT, Wildes JE, Hunt TK. Gender norms, psychometric properties, and validity for the Eating Pathology Symptoms Inventory. Int J Eat Disord 2014;47:85-91.
92. Tang X, Forbush KT, Lui PP. Development and validation of the Chinese-language version of the Eating Pathology Symptoms Inventory. Int J Eat Disord 2015;48:1016-23.
93. Forbes MK, Baillie AJ, Eaton NR et al. A place for sexual functions in an empirical taxonomy of psychopathology. J Sex Res 2017;54:465-85.
94. Forbes MK, Baillie AJ, Schniering CA. Where do sexual dysfunctions fit into the meta-structure of psychopathology? A factor mixture analysis. Arch Sex Behav 2016;45:1883-96.
95. Forbes MK, Schniering CA. Are sexual problems a form of internalizing psychopathology? A structural equation modeling analysis. Arch Sex Behav 2013;42:23-34.
96. Ruggero CJ, Kotov K, Watson D et al. Beyond a single index of mania symptoms: structure and validity of subdimensions. J Affect Disord 2014;161:8-15.
97. Stanton K, Gruber J, Watson D. Basic dimensions defining mania risk: a structural approach. Psychol Assess 2017;29:304-19.
98. Stanton K, Khoo S, Watson D et al. Unique and transdiagnostic features of hypomania/mania and unipolar depression. Clin Psychol Sci 2019;7:471-87.
99. Watson D, Naragon-Gainey K. Personality, emotions, and the emotional disorders. Clin Psychol Sci 2014;2:422-42.
100. Watson D, O'Hara MW, Naragon-Gainey K et al. Development and validation of new anxiety and bipolar symptom scales for an expanded version of the IDAS (the IDAS-II). Assessment 2012;19:399-420.
101. Krueger RF, Chentsova-Dutton YE, Markon KE et al. A cross-cultural study of the structure of comorbidity among common psychopathological syndromes in the general health care setting. J Abnorm Psychol 2003;112:437-47.
102. Simms LJ, Prisciandaro JJ, Krueger RF et al. The structure of depression, anxiety and somatic symptoms in primary care. Psychol Med 2012;42:15-28.
103. Marek RJ, Anderson JL, Tarescavage AM et al. Elucidating somatization in a dimensional model of psychopathology across medical settings. J Abnorm Psychol 2020;129:162-76.
104. Michelini G, Barch DM, Tian Y et al. Delineating and validating higher-order dimensions of psychopathology in the Adolescent Brain Cognitive Development (ABCD) study. Transl Psychiatry 2019;9:261.
105. Sellbom M. Mapping the MMPI-2-RF specific problems scales onto extant psychopathology structures. J Pers Assess 2017;99:341-50.
106. Forbes MT, Sunderland M, Rapee RM et al. A detailed hierarchical model of psychopathology: from individual symptoms up to the general factor of psychopathology. Clin Psychol Sci 2021;9:139-68.
107. Cano-García FJ, Muñoz-Navarro R, Abad AS et al. Latent structure and factor invariance of somatic symptoms in the patient health questionnaire (PHQ-15). J Affect Disord 2020;261:21-9.
108. Budtz-Lilly A, Fink P, Ørnbøl E et al. A new questionnaire to identify bodily distress in primary care: the 'BDS checklist.' J Psychosom Res 2015;78:536-45.
109. Deary IJ. A taxonomy of medically unexplained symptoms. J Psychosom Res 1999;47:51-9.
110. Gierk B, Kohlmann S, Kroenke K et al. The somatic symptom scale-8 (SSS-8): a brief measure of somatic symptom burden. JAMA Intern Med 2014;174:399-407.
111. Leonhart R, De Vroege L, Zhang L et al. Comparison of the factor structure of the Patient Health Questionnaire for somatic symptoms (PHQ-15) in Germany, the Netherlands, and China. A transcultural structural equation modeling (SEM) study. Front Psychiatry 2018;9:240.
112. McNulty JL, Overstreet SR. Viewing the MMPI-2-RF structure through the Personality Psychopathology Five (PSY-5) lens. J Pers Assess 2014;96:151-7.
113. Schmalbach B, Roenneberg C, Hausteiner-Wiehle C et al. Validation of the German version of the Bodily Distress Syndrome 25 checklist in a representative German population sample. J Psychosom Res 2020;132:109991.
114. Thomas ML, Locke DE. Psychometric properties of the MMPI-2-RF Somatic Complaints (RC1) Scale. Psychol Assess 2010;22:492-503.
115. Walentynowicz M, Witthöft M, Raes F et al. Sensory and affective components of symptom perception: a psychometric approach. J Exp Psychopathol 2018;9:1-13.
116. Witthöft M, Hiller W, Loch N et al. The latent structure of medically unexplained symptoms and its relation to functional somatic syndromes. Int J Behav Med 2013;20:172-83.
117. Witthöft M, Fischer S, Jasper F et al. Clarifying the latent structure and correlates of somatic symptom distress: a bifactor model approach. Psychol Assess 2016;28:109-15.
118. Fink P. Syndromes of bodily distress or functional somatic syndromes – Where are we heading. Lecture on the occasion of receiving the Alison Creed award 2017. J Psychosom Res 2017;97:127-30.
119. Petersen MW, Schröder A, Jørgensen T et al. The unifying diagnostic construct of bodily distress syndrome (BDS) was confirmed in the general population. J Psychosom Res 2020;128:109868.
120. Longley SL, Watson D, Noyes R Jr. Assessment of the hypochondriasis domain: the Multidimensional Inventory of Hypochondriacal Traits (MIHT). Psychol Assess 2005:17:3-14.
121. Mulder R. The evolving nosology of personality disorder and its clinical utility. World Psychiatry 2021;20:361-2.
122. Griffith JW, Zinbarg RE, Craske MG et al. Neuroticism as a common dimension in the internalizing disorders. Psychol Med 2010;40:1125-36.
123. Sellbom M, Carragher N, Sunderland M et al. The role of maladaptive personality domains across multiple levels of the HiTOP structure. Personal Ment Health 2020;14:30-50.
124. Soto CJ, John OP. The next Big Five Inventory (BFI-2): developing and assessing a hierarchical model with 15 facets to enhance bandwidth, fidelity, and predictive power. J Pers Soc Psychol 2017;113:117-143.
125. Watson D, Nus E, Wu KD. Development and validation of the Faceted Inventory of the Five-Factor Model (FI-FFM). Assessment 2019;26:17-44.
126. Watters CA, Bagby RM. A meta-analysis of the five-factor internal structure of the Personality Inventory for DSM-5. Psychol Assess 2018;30:1255-60.
127. Mahaffey BL, Watson D, Clark LA et al. Clinical and personality traits in emotional disorders: evidence of a common framework. J Abnorm Psychol 2016;125:758-67.
128. Naragon-Gainey K, Watson D. What lies beyond neuroticism? An examination of the unique contributions of social-cognitive vulnerabilities to internalizing disorders. Assessment 2018;25:143-58.
129. Stanton K, Rozek DC, Stasik-O'Brien SM et al. A transdiagnostic approach to examining the incremental predictive power of emotion regulation and basic personality dimensions. J Abnorm Psychol 2016;125:960-75.
130. Zinbarg RE, Mineka S, Bobova L et al. Testing a hierarchical model of neuroticism and its cognitive facets: latent structure and prospective of first onsets of anxiety and unipolar mood disorders during 3 years in late adolescence. Clin Psychol Sci 2016;4:805-24.
131. Naragon-Gainey K, Simms LJ. Three-way interaction of neuroticism, extraversion, and conscientiousness in the internalizing disorders: evidence of disorder specificity in a psychiatric sample. J Res Pers 2017;70:16-26.
132. Vasey MW, Harbaugh C.N, Lonigan CJ et al. Dimensions of temperament and depressive symptoms: replicating a three-way interaction. J Res Pers 2013;47:908-21.
133. Brandes CM, Tackett JL. Contextualizing neuroticism in the Hierarchical Taxonomy of Psychopathology. J Res Pers 2019;81:238-45.
134. Goldstein BL, Kotov R, Perlman G et al. Trait and facet-level predictors of first-onset depressive and anxiety disorders in a community sample of adolescent girls. Psychol Med 2018;48:1282-90.
135. Jeronimus BF, Kotov R, Riese H et al. Neuroticism's prospective association with mental disorders halves after adjustment for baseline symptoms and psychiatric history, but the adjusted association hardly decays with time: a meta-analysis on 59 longitudinal/prospective studies with 443 313 participants. Psychol Med 2016;46:2883-906.
136. DeYoung CG, Chmielewski M, Clark LA et al. The distinction between symptoms and traits in the Hierarchical Taxonomy of Psychopathology (HiTOP). J Pers (in press).
137. Ormel J, Jeronimus BF, Kotov R et al. Neuroticism and common mental disorders: meaning and utility of a complex relationship. Clin Psychol Rev 2013;33:686-97.
138. Goldstein BL, Perlman G, Eaton NR et al. Testing explanatory models of the interplay between depression, neuroticism, and stressful life events: a dynamic trait-stress generation approach. Psychol Med 2020;50:2780-9.
139. Howe GW, Cimporescu M, Seltzer R et al. Combining stress exposure and stress generation: does neuroticism alter the dynamic interplay of stress, depression, and anxiety following job loss? J Pers 2017:85:553-64.
140. Hettema JM, Neale MC, Myers JM et al. A population-based twin study of the

relationship between neuroticism and internalizing disorders. Am J Psychiatry 2006;163:857-64.
141. South SC, Krueger RF. Marital quality moderates genetic and environmental influences on the internalizing spectrum. J Abnorm Psychol 2008;117:826-37.
142. Nagel M, Jansen PR, Stringer S et al. Meta-analysis of genome-wide association studies for neuroticism in 449,484 individuals identifies novel genetic loci and pathways. Nat Genet 2018;50:920-7.
143. Silverman MH, Wilson S, Ramsay IS et al. Trait neuroticism and emotion neurocircuitry: fMRI evidence for a failure in emotion regulation. Dev Psychopathol 2019;31:1085-99.
144. Watson D, Pennebaker JW. Health complaints, stress, and distress: exploring the central role of negative affectivity. Psychol Rev 1989;96:234-54.
145. Watson D, Clark LA, Harkness AR. Structures of personality and their relevance to psychopathology. J Abnorm Psychol 1994;103:18-31.
146. Deary IJ, Scott S, Wilson JA. Neuroticism, alexithymia and medically unexplained symptoms. Pers Indiv Diff 1997;22:551-64.
147. De Gucht V, Fischler B, Heiser W. Neuroticism, negative affect, and positive affect as determinants of medically unexplained symptoms. Pers Indiv Diff 2004;36:1655-67.
148. Menon V, Shanmuganathan B, Thamizh JS et al. Personality traits such as neuroticism and disability predict psychological distress in medically unexplained symptoms: a three-year experience from a single centre. Personal Ment Health 2018;12:145-54.
149. van Dijk SD, Hanssen D, Naarding P et al. Big Five personality traits and medically unexplained symptoms in later life. Eur Psychiatry 2016;38:23-30.
150. Bailey R, Wells A. Is metacognition a causal moderator of the relationship between catastrophic misinterpretation and health anxiety? A prospective study. Behav Res Ther 2016;78:43-50.
151. Cox BJ, Borger SC, Admundson GJ et al. Dimensions of hypochondriasis and the five-factor model of personality. Pers Indiv Diff 2000;29:99-108.
152. Ferguson E. Hypochondriacal concerns and the five factor model of personality. J Pers 2000;68:705-24.
153. Hollifield M, Tuttle L, Paine S et al. Hypochondriasis and somatization related to personality and attitudes toward self. Psychosomatics 1999;40:387-95.
154. Noyes R Jr, Stuart SP, Langbehn DR et al. Test of an interpersonal model of hypochondriasis. Psychosom Med 2003;65:292-300.
155. Noyes R Jr, Stuart S, Longley SL et al. Hypochondriasis and fear of death. J Nerv Ment Dis 2002;190:503-9.
156. Noyes R Jr, Watson DB, Letuchy EM et al. Relationship between hypochondriacal concerns and personality dimensions and traits in a military population. J Nerv Ment Dis 2005;193:110-8.
157. De Gucht V. Stability of neuroticism and alexithymia in somatization. Compr Psychiatry 2003;44:466-71.
158. Duddu V, Isaac MK, Chaturvedi SK. Somatization, somatosensory amplification, attribution styles and illness behaviour: a review. Int Rev Psychiatry 2006;18:25-33.
159. Kushwaha V, Chadda RK, Mehta M. Psychotherapeutic intervention in somatisation disorder: results of a controlled study from India. Psychol Health Med 2013;18:445-50.
160. Sheehan B, Banerjee S. Review: somatization in the elderly. Int J Geriatr Psychiatry 1999;14:1044-9.
161. Longley S, Calamari JE, Noyes R et al. Health anxiety (hypochondriasis): an emotional disorder in an alternative taxonomy. Curr Psychiatry Rev 2014;10:3-13.
162. Cosgrove VE, Rhee SH, Gelhorn HL et al. Structure and etiology of co-occurring internalizing and externalizing disorders in adolescents. J Abnorm Child Psychol 2011;39:109-23.
163. Kendler K, Myers J. The boundaries of the internalizing and externalizing genetic spectra in men and women. Psychol Med 2014;44:647-55.
164. Lahey BB, Van Hulle CA, Singh AL et al. Higher-order genetic and environmental structure of prevalent forms of child and adolescent psychopathology. Arch Gen Psychiatry 2011;68:181-9.
165. Mosing MA, Gordon SD, Medland SE et al. Genetic and environmental influences on the co-morbidity between depression, panic disorder, agoraphobia, and social phobia: a twin study. Depress Anxiety 2009;26:1004-11.
166. Tackett JL, Lahey BB, Van Hulle C et al. Common genetic influences on negative emotionality and a general psychopathology factor in childhood and adolescence. J Abnorm Psychol 2013;122:1142-53.
167. Waldman ID, Poore HE, van Hulle C et al. External validity of a hierarchical dimensional model of child and adolescent psychopathology: tests using confirmatory factor analyses and multivariate behavior genetic analyses. J Abnorm Psychol 2016;125:1053-66.
168. Hettema JM, Prescott CA, Myers JM et al. The structure of genetic and environmental risk factors for anxiety disorders in men and women. Arch Gen Psychiatry 2005;62:182-9.
169. Kendler K, Prescott CA, Myers J et al. The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. Arch Gen Psychiatry 2003;60:929-37.
170. Waszczuk MA, Zavos HM, Gregory AM et al. The phenotypic and etiological structure of depression and anxiety disorder symptoms in childhood, adolescence and young adulthood. JAMA Psychiatry 2014;71:905-16.
171. Bulik CM, Thornton LM, Root TL et al. Understanding the relation between anorexia nervosa and bulimia nervosa in a Swedish national twin sample. Biol Psychiatry 2010;67:71-7.
172. O'Connor SM, Beam CR, Luo X et al. Genetic and environmental associations between body dissatisfaction, weight preoccupation, and binge eating: evidence for a common factor with differential loadings across symptom type. Int J Eat Disord 2016;50:157-61.
173. Waszczuk MA, Waaktaar T, Eley TC et al. Etiological influences on continuity and co-occurrence of eating disorders symptoms across adolescence and emerging adulthood. Int J Eat Disord 2019;52:554-63.
174. Kendler K, Walters EE, Neale MC et al. The structure of the genetic and environmental risk factors for six major psychiatric disorders in women: phobia, generalized anxiety disorder, panic disorder, bulimia, major depression, and alcoholism. Arch Gen Psychiatry 1995;52:374-83.
175. Silberg JL, Bulik CM. The developmental association between eating disorders symptoms and symptoms of depression and anxiety in juvenile twin girls. J Child Psychol Psychiatry 2005;46:1317-26.
176. Thornton LM, Welch E, Munn-Chernoff MA et al. Anorexia nervosa, major depression, and suicide attempts: shared genetic factors. Suicide Life Threat Behav 2016;46:525-34.
177. Wade TD, Fairweather-Schmidt AK, Zhu G et al. Does shared genetic risk contribute to the co-occurrence of eating disorders and suicidality? Int J Eat Disord 2015;48:684-91.
178. Cederlöf M, Thornton LM, Baker J et al. Etiological overlap between obsessive-compulsive disorder and anorexia nervosa: a longitudinal cohort, multigenerational family and twin study. World Psychiatry 2015;14:333-8.
179. McGuffin P, Rijsdijk F, Andrew M et al. The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. Arch Gen Psychiatry 2003;60:497-502.
180. Smoller JW, Finn CT. Family, twin, and adoption studies of bipolar disorder. Am J Med Genet C Semin Med Genet 2003;123C:48-58.
181. Song J, Bergen SE, Kuja-Halkola R et al. Bipolar disorder and its relation to major psychiatric disorders: a family-based study in the Swedish population. Bipolar Disord 2015;17:184-93.
182. Cardno AG, Owen MJ. Genetic relationships between schizophrenia, bipolar disorder, and schizoaffective disorder. Schizophr Bull 2014;40:504-15.
183. Kläning U, Trumbetta SL, Gottesman II et al. A Danish twin study of schizophrenia liability: investigation from interviewed twins for genetic links to affective psychoses and for cross-cohort comparisons. Behav Genet 2016;46:193-204.
184. Lichtenstein P, Yip BH, Björk C et al. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. Lancet 2009;373:234-39.
185. Pettersson E, Larsson H, Lichtenstein P. Common psychiatric disorders share the same genetic origin: a multivariate sibling study of the Swedish population. Mol Psychiatry 2016;21:717-21.
186. Gillespie N, Zhu G, Heath A et al. The genetic aetiology of somatic distress. Psychol Med 2000;30:1051-61.
187. Hansell N, Wright M, Medland S et al. Genetic co-morbidity between neuroticism, anxiety/depression and somatic distress in a population sample of adolescent and young adult twins. Psychol Med 2012;42:1249-60.
188. Kato K, Sullivan PF, Evengård B et al. A population-based twin study of functional somatic syndromes. Psychol Med 2009;39:497-505.
189. Ask H, Waaktaar T, Seglem KB et al. Common etiological sources of anxiety, depression, and somatic complaints in adolescents: a multiple rater twin study. J Abnorm Child Psychol 2016;44:101-14.
190. Ball HA, Siribaddana SH, Sumathipala A al. Genetic and environmental contributions to the overlap between psychological, fatigue and somatic symptoms: a twin study in Sri Lanka. Twin Res Hum Genet 2011;14:53-63.
191. Khan WU, Michelini G, Battaglia M. Twin studies of the covariation of pain with depression and anxiety: a systematic review and re-evaluation of critical needs. Neurosci Biobehav Rev 2020;111:135-48.
192. Wray NR, Lee SH, Mehta D et al. Research review: polygenic methods and

their application to psychiatric traits. J Child Psychol Psychiatry 2014;55:1068-87.
193. Howard DM, Adams MJ, Clarke T-K et al. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. Nature Neurosci 2019;22:343.
194. Levey DF, Gelernter J, Polimanti R et al. Reproducible genetic risk loci for anxiety: results from ~200,000 participants in the Million Veteran Program. Am J Psychiatry 2020;177:223-32.
195. Stein MB, Levey DF, Cheng Z et al. Genomic characterization of posttraumatic stress disorder in a large US military veteran sample. bioRxiv 2019;764001.
196. Ward J, Lyall LM, Bethlehem RA et al. Novel genome-wide associations for anhedonia, genetic correlation with psychiatric disorders, and polygenic association with brain structure. Transl Psychiatry 2019;9:1-9.
197. Lee PH, Anttila V, Won H et al. Genomic relationships, novel loci, and pleiotropic mechanisms across eight psychiatric disorders. Cell 2019;179:1469-82.e11.
198. Waldman ID, Poore HE, Luningham JM et al. Testing structural models of psychopathology at the genomic level. World Psychiatry 2020;19:350-9.
199. Levey DF, Stein MB, Wendt FR et al. GWAS of depression phenotypes in the Million Veteran Program and meta-analysis in more than 1.2 million participants yields 178 independent risk loci. medRxiv 2020; 20100685.
200. Watson HJ, Yilmaz, Z, Thornton LM et al. Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. Nat Genet 2019;51:1207-14.
201. Stahl EA, Breen G, Forstner AJ et al. Genome-wide association study identifies 30 loci associated with bipolar disorder. Nat Genet 2019;51:793-803.
202. Coombes B, Markota M, Mann J et al. Dissecting clinical heterogeneity of bipolar disorder using multiple polygenic risk scores. Transl Psychiatry 2020; 10:314.
203. Morneau-Vaillancourt G, Coleman JR, Purves KL et al. The genetic and environmental hierarchical structure of anxiety and depression in the UK Biobank. Depress Anxiety 2020;37:512-20.
204. Thorp JG, Campos AI, Grotzinger AD et al. Symptom-level genetic modelling identifies novel risk loci and unravels the shared genetic architecture of anxiety and depression. medRxiv 2020; 20057653.
205. Hill WD, Weiss A, Liewald DC et al. Genetic contributions to two special factors of neuroticism are associated with affluence, higher intelligence, better health, and longer life. Mol Psychiatry 2020; 25:3034-52.
206. Nagel M, Watanabe K, Stringer S et al. Item-level analyses reveal genetic heterogeneity in neuroticism. Nat Commun 2018;9:905.
207. Johnston KJ, Adams MJ, Nicholl BI et al. Genome-wide association study of multisite chronic pain in UK Biobank. PLoS Genet 2019;15:e1008164.
208. Leppert B, Millard LA, Riglin L et al. A cross-disorder PRS-pheWAS of 5 major psychiatric disorders in UK Biobank. PLoS Genet 2020;16:e1008185.
209. O'Sullivan JW, Ioannidis J. Reproducibility in the UK Biobank of genome-wide significant signals discovered in earlier genome-wide association studies. medRxiv 2020;20139576.
210. Okbay A, Baselmans BM, De Neve J-E et al. Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses. Nat Genet 2016; 48:624-33.
211. Otowa T, Hek K, Lee M et al. Meta-analysis of genome-wide association studies of anxiety disorders. Mol Psychiatry 2016;21:1391-9.
212. Kendler K, Myers JM, Maes HH et al. The relationship between the genetic and environmental influences on common internalizing psychiatric disorders and mental well-being. Behav Genet 2011;41:641-50.
213. Abbott CS, Forbes MK, Anker JJ. Association of childhood adversity with differential susceptibility of transdiagnostic psychopathology to environmental stress in adulthood. JAMA Network Open 2018;1:e185354.
214. Conway CC, Hammen C, Brennan PA. Expanding stress generation theory: test of a transdiagnostic model. J Abnorm Psychol 2012;121:754-66.
215. Conway CC, Raposa EB, Hammen C et al. Transdiagnostic pathways from early social stress to psychopathology: a 20-year prospective study. J Child Psychol Psychiatry 2018;59:855-62.
216. Vachon DD, Krueger RF, Rogosch FA et al. Assessment of the harmful psychiatric and behavioral effects of different forms of child maltreatment. JAMA Psychiatry 2015;72:1135-42.
217. Forbes MK, Magson NR, Rapee RM. Evidence that different types of peer victimization have equivalent associations with transdiagnostic psychopathology in adolescence. J Youth Adolesc 2020;49:590-604.
218. Snyder HR, Young JF, Hankin BL. Strong homotypic continuity in common psychopathology-, internalizing-, and externalizing-specific factors over time in adolescents. Clin Psychol Sci 2017;5:98-110.
219. Jenness JL, Peverill M, King KM et al. Dynamic associations between stressful life events and adolescent internalizing psychopathology in a multiwave longitudinal study. J Abnorm Psychol 2019;128:596-609.
220. Rodriguez-Seijas C, Stohl M, Hasin DS et al. Transdiagnostic factors and mediation of the relationship between perceived racial discrimination and mental disorders. JAMA Psychiatry 2015;72:706-13.
221. Witthöft M, Hiller W. Psychological approaches to origins and treatments of somatoform disorders. Annu Rev Clin Psychol 2010;6:257-83.
222. Joormann J, Gotlib IH. Emotion regulation in depression: relation to cognitive inhibition. Cogn Emot 2010;24:281-98.
223. Knight MJ, Baune BT. Cognitive dysfunction in major depressive disorder. Curr Opin Psychiatry 2018;31:26-31.
224. MacQueen GM, Memedovich KA. Cognitive dysfunction in major depression and bipolar disorder: assessment and treatment options. Psychiatry Clin Neurosci 2017;71:18-27.
225. Scult MA, Paulli AR, Mazure ES et al. The association between cognitive function and subsequent depression: a systematic review and meta-analysis. Psychol Med 2017;47:1-17.
226. Snyder HR. Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review. Psychol Bull 2013;139:81-132.
227. Malarbi S, Abu-Rayya HM, Muscara F et al. Neuropsychological functioning of childhood trauma and post-traumatic stress disorder: a meta-analysis. Neurosci Biobehav Rev 2017;72:68-86.
228. Schuitevoerder S, Rosen JW, Twamley EW et al. A meta-analysis of cognitive functioning in older adults with PTSD. J Anxiety Disord 2013;27:550-8.
229. Buckley TC, Blanchard EB, Neill WT. Information processing and PTSD: a review of the empirical literature. Clin Psychol Rev 2000;20:1041-65.
230. Hayes JP, VanElzakker MB, Shin LM. Emotion and cognition interactions in PTSD: a review of neurocognitive and neuroimaging studies. Front Integr Neurosci 2012;6:89.
231. Nawijn L, van Zuiden M, Frijling JL et al. Reward functioning in PTSD: a systematic review exploring the mechanisms underlying anhedonia. Neurosci Biobehav Rev 2015;51:189-204.
232. Alves MR, Pereira VM, Machado S et al. Cognitive functions in patients with panic disorder: a literature review. Braz J Psychiatry 2013;35:193-200.
233. Cremers HR, Roelofs K. Social anxiety disorder: a critical overview of neurocognitive research. Wiley Interdiscip Rev Cogn Sci 2016;7:218-32.
234. Eysenck MW, Derakshan N. New perspectives in attentional control theory. Pers Individ Diff 2011;50:955-90.
235. Muller J, Roberts JE. Memory and attention in obsessive-compulsive disorder: a review. J Anxiety Disord 2005;19:1-28.
236. O'Sullivan K, Newman EF. Neuropsychological impairments in panic disorder: a systematic review. J Affect Disord 2014;167:268-84.
237. Benzina N, Mallet L, Burguière E et al. Cognitive dysfunction in obsessive-compulsive disorder. Curr Psychiatry Rep 2016;18:80.
238. Gruner P, Pittenger C. Cognitive inflexibility in obsessive-compulsive disorder. Neuroscience 2017;345:243-55.
239. Hezel DM, McNally RJ. A theoretical review of cognitive biases and deficits in obsessive-compulsive disorder. Biol Psychol 2016;121:221-32.
240. Plana I, Lavoie MA, Battaglia M et al. A meta-analysis and scoping review of social cognition performance in social phobia, posttraumatic stress disorder and other anxiety disorders. J Anxiety Disord 2014;28:169-77.
241. Kanakam N, Treasure J. A review of cognitive neuropsychiatry in the taxonomy of eating disorders: state, trait, or genetic? Cogn Neuropsychiatry 2013; 18:83-114.
242. Kittel R, Brauhardt A, Hilbert A. Cognitive and emotional functioning in binge-eating disorder: a systematic review. Int J Eat Disord 2015;48:535-54.
243. Roberts ME, Tchanturia K, Stahl D et al. A systematic review and meta-analysis of set-shifting ability in eating disorders. Psychol Med 2007;37:1075-84.
244. Lena SM, Fiocco AJ, Leyenaar JK. The role of cognitive deficits in the development of eating disorders. Neuropsychol Rev 2004;14:99-113.
245. Lopez C, Tchanturia K, Stahl D et al. Central coherence in eating disorders: a systematic review. Psychol Med 2008;38:1393-404.
246. Fisher TD, Davis CM, Yarber WL (eds). Handbook of sexuality-related measures. New York: Routledge, 2013.
247. Peixoto MM, Nobre P. Cognitive schemas activated in sexual context: a comparative study with homosexual and heterosexual men and women, with and without sexual problems. Cogn Ther Res 2015;39:390-402.
248. Becker SP, Langberg JM, Luebbe AM et al. Sluggish cognitive tempo is associated with academic functioning and internalizing symptoms in college students with and without attention-deficit/hyperactivity disorder. J Clin Psychol 2014;70:388-403.

249. Jacobson LA, Geist M, Mahone EM. Sluggish cognitive tempo, processing speed, and internalizing symptoms: the moderating effect of age. J Abnorm Child Psychol 2018;46:127-35.
250. Bloemen AJ, Oldehinkel AJ, Laceulle OM et al. The association between executive functioning and psychopathology: general or specific? Psychol Med 2018;48:1787-94.
251. Bora E, Pantelis C. Meta-analyses of cognitive impairment in first-episode bipolar disorder: comparisons with first-episode schizophrenia and healthy controls. Schizophr Bull 2015;41:1095-104.
252. Rock PL, Roiser JP, Riedel WJ et al. Cognitive impairment in depression: a systematic review and meta-analysis. Psychol Med 2014;44:2029-40.
253. Solé B, Martínez-Arán A, Torrent C et al. Are bipolar II patients cognitively impaired? A systematic review. Psychol Med 2011;41:1791-803.
254. Alloy LB, Olino T, Freed RD et al. Role of reward sensitivity and processing in major depressive and bipolar spectrum disorders. Behav Ther 2016;47:600-21.
255. Johnson SL, Edge MD, Holmes MK et al. The behavior activation system and mania. Annu Rev Clin Psychol 2012;8:243-67.
256. de Vroege L, Timmermans A, Kop WJ et al. Neurocognitive dysfunctioning and the impact of comorbid depression and anxiety in patients with somatic symptom and related disorders: a cross-sectional clinical study. Psychol Med 2018;48:1803-13.
257. Lim SL, Kim JH. Cognitive processing of emotional information in depression, panic, and somatoform disorder. J Abnorm Psychol 2005;114:50-61.
258. Amad A, Radua J, Vaiva G et al. Similarities between borderline personality disorder and post traumatic stress disorder: evidence from resting-state meta-analysis. Neurosci Biobehav Rev 2019;105:52-9.
259. Schmaal L, Hibar DP, Sämann PG et al. Cortical abnormalities in adults and adolescents with major depression based on brain scans from 20 cohorts worldwide in the ENIGMA Major Depressive Disorder Working Group. Mol Psychiatry 2017;22:900-9.
260. Stevens JS, Jovanovic T. Role of social cognition in post-traumatic stress disorder: a review and meta-analysis. Genes Brain Behav 2019;18:e12518.
261. Tang S, Lu L, Zhang L et al. Abnormal amygdala resting-state functional connectivity in adults and adolescents with major depressive disorder: a comparative meta-analysis. EBioMedicine 2018;36:436-45.
262. Siehl S, King JA, Burgess N et al. Structural white matter changes in adults and children with posttraumatic stress disorder: a systematic review and meta-analysis. Neuroimage Clin 2018;19:581-98.
263. Bromis K, Calem M. Reinders AA et al. Meta-analysis of 89 structural MRI studies in posttraumatic stress disorder and comparison with major depressive disorder. Am J Psychiatry 2018;175:989-98.
264. Jiang J, Zhao Y-J, Hu X-Y et al. Microstructural brain abnormalities in medication-free patients with major depressive disorder: a systematic review and meta-analysis of diffusion tensor imaging. J Psychiatry Neurosci 2017;42:150-63.
265. Madonna D, Delvecchio G, Soares JC et al. Structural and functional neuroimaging studies in generalized anxiety disorder: a systematic review. Braz J Psychiatry 2019;41:336-62.
266. Binelli C, Subirà S, Batalla A et al. Common and distinct neural correlates of facial emotion processing in social anxiety disorder and Williams syndrome: a systematic review and voxel-based meta-analysis of functional resonance imaging studies. Neuropsychologia 2014;64:205-17.
267. Doruyter AG, Dupont P, Stein DJ et al. Nuclear neuroimaging in social anxiety disorder: a review. J Nucl Med 2018;59:1794-800.
268. Duval ER, Javanbakht A, Liberzon I. Neural circuits in anxiety and stress disorders: a focused review. Ther Clin Risk Manag 2015;11:115-26.
269. Frydman I, de Salles Andrade JB, Vigne P et al. Can neuroimaging provide reliable biomarkers for obsessive-compulsive disorder? A narrative review. Curr Psychiatry Rep 2016;18:90.
270. Gentili C, Benvenuti SM, Lettieri G et al. ROI and phobias: the effect of ROI approach on an ALE meta-analysis of specific phobias. Hum Brain Mapp 2019;40:1814-28.
271. Parmar A, Sarkar S. Neuroimaging studies in obsessive compulsive disorder: a narrative review. Indian J Psychol Med 2016;38:386-94.
272. Thorsen AL, Hagland P, Radua J et al. Emotional processing in obsessive-compulsive disorder: a systematic review and meta-analysis of 25 functional neuroimaging studies. Biol Psychiatry Cogn Neurosci Neuroimaging 2018;3:563-71.
273. Gürsel DA, Avram M, Sorg C et al. Frontoparietal areas link impairments of large-scale intrinsic brain networks with aberrant fronto-striatal interactions in OCD: a meta-analysis of resting-state functional connectivity. Neurosci Biobehav Rev 2018;87:151-60.
274. Kim YK, Yoon HK. Common and distinct brain networks underlying panic and social anxiety disorders. Prog Neuropsychopharmacol Biol Psychiatry 2018;80:115-22.
275. Bas-Hoogendam JM, van Steenbergen H, Tissier RL et al. Subcortical brain volumes, cortical thickness and cortical surface area in families genetically enriched for social anxiety disorder – A multiplex multigenerational neuroimaging study. EBioMedicine 2018;36:410-28.
276. Berner LA, Winter SR, Matheson BE et al. Behind binge eating: a review of food-specific adaptations of neurocognitive and neuroimaging tasks. Physiol Behav 2017;176:59-70.
277. Donnelly B, Touyz S, Hay P et al. Neuroimaging in bulimia nervosa and binge eating disorder: a systematic review. J Eat Disord 2018;6:3.
278. Frank GKW. Neuroimaging and eating disorders. Curr Opin Psychiatry 2019; 32:478-83.
279. McClelland J, Dalton B, Kekic M et al. A systematic review of temporal discounting in eating disorders and obesity: behavioural and neuroimaging findings. Neurosci Biobehav Rev 2016;71:506-28.
280. Berner LA, Brown TA, Lavender JM et al. Neuroendocrinology of reward in anorexia nervosa and bulimia nervosa: beyond leptin and ghrelin. Mol Cell Endocrinol 2019;497:110320.
281. Frank GK. Advances from neuroimaging studies in eating disorders. CNS Spectr 2015;20:391-400.
282. Mitelman SA. Transdiagnostic neuroimaging in psychiatry: a review. Psychiatry Res 2019;277:23-38.
283. Steward T, Menchon JM, Jiménez-Murcia S et al. Neural network alterations across eating disorders: a narrative review of fMRI studies. Curr Neuropharmacol 2018;16:1150-63.
284. Cacioppo S. Neuroimaging of female sexual desire and hypoactive sexual desire disorder. Sex Med Rev 2017;5:434-44.
285. Poeppl TB, Langguth B, Laird AR et al. Meta-analytic evidence for neural dysactivity underlying sexual dysfunction. J Sex Med 2019;16:614-7.
286. Chen CH, Suckling J, Lennox BR et al. A quantitative meta-analysis of fMRI studies in bipolar disorder. Bipolar Disord 2011;13:1-15.
287. Duarte JA, de Araújo e Silva JQ, Goldani AA et al. Neurobiological underpinnings of bipolar disorder focusing on findings of diffusion tensor imaging: a systematic review. Braz J Psychiatry 2016;38:167-75.
288. Toma S, MacIntosh BJ, Swardfager W et al. Cerebral blood flow in bipolar disorder: a systematic review. J Affect Disord 2018;241:505-13.
289. Wise T, Radua J, Nortje G et al. Voxel-based meta-analytical evidence of structural disconnectivity in major depression and bipolar disorder. Biol Psychiatry 2016;79:293-302.
290. Boeckle M, Schrimpf M, Liegl G et al. Neural correlates of somatoform disorders from a meta-analytic perspective on neuroimaging studies. Neuroimage Clin 2016;11:606-13.
291. Allen JJ, Coan JA, Nazarian M. Issues and assumptions on the road from raw signals to metrics of frontal EEG asymmetry in emotion. Biol Psychol 2004;67:183-218.
292. Coan JA, Allen JJ. Frontal EEG asymmetry as a moderator and mediator of emotion. Biol Psychol 2004;67:7-49.
293. Davidson RJ. Affective style and affective disorders: perspectives from affective neuroscience. Cogn Emot 1998;12:307-30.
294. Thibodeau R, Jorgensen RS, Kim S. Depression, anxiety, and resting frontal EEG asymmetry: a meta-analytic review. J Abnorm Psychol 2006;115:715-29.
295. van der Vinne N, Vollebregt MA, van Putten MJ et al. Frontal alpha asymmetry as a diagnostic marker in depression: fact or fiction? A meta-analysis. Neuroimage Clin 2017;16:79-87.
296. Feldmann L, Piechaczek CE, Grünewald BD et al. Resting frontal EEG asymmetry in adolescents with major depression: impact of disease state and comorbid anxiety disorder. Clin Neurophysiol 2018;129:2577-85.
297. Grünewald BD, Greimel E, Trinkl M et al. Resting frontal EEG asymmetry patterns in adolescents with and without major depression. Biol Psychol 2018;132:212-6.
298. Kemp AH, Griffiths K, Felmingham KL et al. Disorder specificity despite comorbidity: resting EEG alpha asymmetry in major depressive disorder and post-traumatic stress disorder. Biol Psychol 2010;85:350-4.
299. Shankman SA, Nelson BD, Sarapas C et al. A psychophysiological investigation of threat and reward sensitivity in individuals with panic disorder and/or major depressive disorder. J Abnorm Psychol 2013;122:322-38.
300. Stewart JL, Bismark AW, Towers DN et al. Resting frontal EEG asymmetry as an endophenotype for depression risk: sex-specific patterns of frontal brain asymmetry. J Abnorm Psychol 2010;119:502-12.
301. Stewart JL, Coan JA, Towers DN et al. Frontal EEG asymmetry during emotional challenge differentiates individuals with and without lifetime major depressive disorder. J Affect Disord 2011;129:167-74.
302. Stewart JL, Coan JA, Towers DN et al. Resting and task-elicited prefrontal EEG alpha asymmetry in depression: support for the capability model. Psy-

chophysiology 2014;51:446-55.
303. Wiedemann G, Pauli P, Dengler W et al. Frontal brain asymmetry as a biological substrate of emotions in patients with panic disorders. Arch Gen Psychiatry 1999;56:78-84.
304. Ischebeck M, Endrass T, Simon D et al. Altered frontal EEG asymmetry in obsessive-compulsive disorder. Psychophysiology 2014;51:596-601.
305. Nusslock R, Harmon-Jones E, Alloy LB et al. Elevated left mid-frontal cortical activity prospectively predicts conversion to bipolar I disorder. J Abnorm Psychol 2012;121:592-601.
306. Proudfit GH. The reward positivity: from basic research on reward to a biomarker for depression. Psychophysiology 2015;52:449-59.
307. Keren H, O'Callaghan G, Vidal-Ribas P et al. Reward processing in depression: a conceptual and meta-analytic review across fMRI and EEG studies. Am J Psychiatry 2018;175:1111-20.
308. Moran TP, Schroder HS, Kneip C et al. Meta-analysis and psychophysiology: a tutorial using depression and action-monitoring event-related potentials. Int J Psychophysiol 2017;111:17-32.
309. Bress JN, Meyer A, Hajcak G. Differentiating anxiety and depression in children and adolescents: evidence from event-related brain potentials. J Clin Child Adolesc Psychol 2015;44:238-49.
310. Bress JN, Smith E, Foti D et al. Neural response to reward and depressive symptoms in late childhood to early adolescence. Biol Psychol 2012;89:156-62.
311. Brush CJ, Ehmann PJ, Hajcak G et al. Using multilevel modeling to examine blunted neural responses to reward in major depression. Biol Psychiatry Cogn Neurosci Neuroimaging 2018;3:1032-9.
312. Burkhouse KL, Gorka SM, Afshar K et al. Neural reactivity to reward and internalizing symptom dimensions. J Affect Disord 2017;217:73-9.
313. Foti D, Carlson JM, Sauder CL et al. Reward dysfunction in major depression: multimodal neuroimaging evidence for refining the melancholic phenotype. NeuroImage 2014;101:50-8.
314. Foti D, Hajcak G. Depression and reduced sensitivity to non-rewards versus rewards: evidence from event-related potentials. Biol Psychol 2009;81:1-8.
315. Liu WH, Wang LZ, Shang HR et al. The influence of anhedonia on feedback negativity in major depressive disorder. Neuropsychologia 2014;53:213-20.
316. Whitton AE, Kakani P, Foti D et al. Blunted neural responses to reward in remitted major depression: a high-density event-related potential study. Biol Psychiatry Cogn Neurosci Neuroimaging 2016;1:87-95.
317. Kessel EM, Kujawa A, Proudfit GH et al. Neural reactivity to monetary rewards and losses differentiates social from generalized anxiety in children. J Child Psychol Psychiatry 2014;56:792-800.
318. Foti D, Kotov R, Klein DN et al. Abnormal neural sensitivity to monetary gains versus losses among adolescents at risk for depression. J Abnorm Child Psychol 2011;39:913-24.
319. Kujawa A, Proudfit GH, Klein DN. Neural reactivity to rewards and losses in offspring of mothers and fathers with histories of depressive and anxiety disorders. J Abnorm Psychol 2014;123:287-97.
320. Bress JN, Foti D, Kotov R et al. Blunted neural response to rewards prospectively predicts depression in adolescent girls. Psychophysiology 2013;50:74-81.
321. Nelson BD, Perlman G, Klein DN et al. Blunted neural response to rewards as a prospective predictor of the development of depression in adolescent girls. Am J Psychiatry 2016;173:1223-30.
322. Weinberg A, Meyer A, Hale-Rude E et al. Error-related negativity (ERN) and sustained threat: conceptual framework and empirical evaluation in an adolescent sample. Psychophysiology 2016;53:372-85.
323. Moser JS, Moran TP, Schroder HS et al. On the relationship between anxiety and error monitoring: a meta-analysis and conceptual framework. Front Hum Neurosci 2013;7:466.
324. Barker TV, Troller-Renfree S, Pine DS et al. Individual differences in social anxiety affect the salience of errors in social contexts. Cogn Affect Behav Neurosci 2015;15:723-35.
325. Carrasco M, Harbin SM, Nienhuis JK et al. Increased error-related brain activity in youth with obsessive-compulsive disorder and unaffected siblings. Depress Anxiety 2013;30:39-46.
326. Endrass T, Riesel A, Kathmann N et al. Performance monitoring in obsessive-compulsive disorder and social anxiety disorder. J Abnorm Psychol 2014;123:705-14.
327. Harrewijn A, Schmidt LA, Westenberg PM et al. Electrocortical measures of information processing biases in social anxiety disorder: a review. Biol Psychol 2017;129:324-48.
328. Weinberg A, Klein DN, Hajcak G. Increased error-related brain activity distinguishes generalized anxiety disorder with and without comorbid major depressive disorder. J Abnorm Psychol 2012;121:885-96.
329. Weinberg A, Olvet DM, Hajcak G. Increased error-related brain activity in generalized anxiety disorder. Biol Psychol 2010;85:472-80.
330. Xiao Z, Wang J, Zhang M et al. Error-related negativity abnormalities in generalized anxiety disorder and obsessive-compulsive disorder. Prog Neuropsychopharmacol Biol Psychiatry 2011;35:265-72.
331. Riesel A, Endrass T, Kaufmann C et al. Overactive error-related brain activity as a candidate endophenotype for obsessive-compulsive disorder: evidence from unaffected first-degree relatives. Am J Psychiatry 2011;168:317-24.
332. Riesel A, Klawohn J, Grützmann R et al. Error-related brain activity as a transdiagnostic endophenotype for obsessive-compulsive disorder, anxiety and substance use disorder. Psychol Med 2019;49:1207-17.
333. Meyer A, Hajcak G, Torpey-Newman DC et al. Enhanced error-related brain activity in children predicts the onset of anxiety disorders between the ages of 6 and 9. J Abnorm Psychol 2015;124:266-74.
334. Meyer A, Nelson B, Perlman G et al. A neural biomarker, the error-related negativity, predicts the first onset of generalized anxiety disorder in a large sample of adolescent females. J Child Psychol Psychiatry 2018;59:1162-70.
335. Riesel A, Goldhahn S, Kathmann N. Hyperactive performance monitoring as a transdiagnostic marker: results from health anxiety in comparison to obsessive-compulsive disorder. Neuropsychologia 2017;96:1-8.
336. Berryman C, Wise V, Stanton TR et al. A case-matched study of neurophysiological correlates to attention/working memory in people with somatic hypervigilance. J Clin Exp Neuropsychol 2017;39:84-99.
337. Kemp AH, Pe Benito L, Quintana DS et al. Impact of depression heterogeneity on attention: an auditory oddball event related potential study. J Affect Disord 2010;123:202-7.
338. Morsel AM, Morrens M, Dhar M et al. Systematic review of cognitive event related potentials in euthymic bipolar disorder. Clin Neurophysiol 2018;129:1854-65.
339. Nan C, Wang G, Wang H et al. The P300 component decreases in a bimodal oddball task in individuals with depression: an event-related potentials study. Clin Neurophysiol 2018;129:2525-33.
340. Yu Y, Jiang C, Xu H et al. Impaired cognitive control of emotional conflict in trait anxiety: a preliminary study based on clinical and non-clinical individuals. Front Psychiatry 2018;9:120.
341. Yue L, Tang Y, Kang Q et al. Deficits in response inhibition on varied levels of demand load in anorexia nervosa: an event-related potentials study. Eat Weight Disord 2020;25:231-40.
342. Bernat EM, Ellis JS, Bachman MD et al. P3 amplitude reductions are associated with shared variance between internalizing and externalizing psychopathology. Psychophysiology 2020;57:e13618.
343. Chami R, Cardi V, Lautarescu A et al. Neural responses to food stimuli among individuals with eating and weight disorders: a systematic review of event-related potentials. Int Rev Psychiatry 2019;31:318-31.
344. Harrewijn A, van der Molen MJ, van Vliet IM et al. Behavioral and EEG responses to social evaluation: a two-generation family study on social anxiety. Neuroimage Clin 2018;17:549-62.
345. Javanbakht A, Liberzon I, Amirsadri A et al. Event-related potential studies of post-traumatic stress disorder: a critical review and synthesis. Biol Mood Anxiety Disord 2011;1:5.
346. Lobo I, Portugal LC, Figueira I et al. EEG correlates of the severity of post-traumatic stress symptoms: a systematic review of the dimensional PTSD literature. J Affect Disord 2015;183:210-20.
347. Hill KE, South SC, Egan RP et al. Abnormal emotional reactivity in depression: contrasting theoretical models using neurophysiological data. Biol Psychol 2019;141:35-43.
348. Klawohn J, Santopetro NJ, Meyer A et al. Reduced P300 in depression: evidence from a flanker task and impact on ERN, CRN, and Pe. Psychophysiology 2020;57:e13520.
349. Nelson BD, Perlman G, Hajcak G et al. Familial risk for distress and fear disorders and emotional reactivity in adolescence: an event-related potential investigation. Psychol Med 2015;45:2545-56.
350. Weinberg A, Hajcak G. Electrocortical evidence for vigilance-avoidance in generalized anxiety disorder. Psychophysiology 2011;48:842-51.
351. Whalen DJ, Gilbert KE, Kelly D et al. Preschool-onset major depressive disorder is characterized by electrocortical deficits in processing pleasant emotional pictures. J Abnorm Child Psychol 2020;48:91-108.
352. Michalowski JM, Melzig CA, Weike AI et al. Brain dynamics in spider-phobic individuals exposed to phobia-relevant and other emotional stimuli. Emotion 2009;9:306-15.
353. Miltner WH, Trippe RH, Krieschel S et al. Event-related brain potentials and

affective responses to threat in spider/snake-phobic and non-phobic subjects. Int J Psychophysiol 2005;57:43-52.
354. Moser JS, Huppert JD, Duval E et al. Face processing biases in social anxiety: an electrophysiological study. Biol Psychol 2008;78:93-103.
355. Pauli P, Dengler W, Wiedemann G et al. Behavioral and neurophysiological evidence for altered processing of anxiety-related words in panic disorder. J Abnorm Psychol 1997;106:213-20.
356. Brandys MK, Kas MJ, van Elburg AA et al. A meta-analysis of circulating BDNF concentrations in anorexia nervosa. World J Biol Psychiatry 2011;12:444-54.
357. Brunoni AR, Lopes M, Fregni F. A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression. Int J Neuropsychopharmacol 2008;11:1169-80.
358. Fernandes BS, Molendijk ML, Köhler CA et al. Peripheral brain-derived neurotrophic factor (BDNF) as a biomarker in bipolar disorder: a meta-analysis of 52 studies. BMC Med 2015;13:289.
359. Monteleone P, Maj M. Dysfunctions of leptin, ghrelin, BDNF and endocannabinoids in eating disorders: beyond the homeostatic control of food intake. Psychoneuroendocrinology 2013;38:312-30.
360. Munkholm K, Vinberg M, Kessing LV. Peripheral blood brain-derived neurotrophic factor in bipolar disorder: a comprehensive systematic review and meta-analysis. Mol Psychiatry 2016;21:216-28.
361. Salas-Magaña M, Tovilla-Zárate CA, González-Castro TB et al. Decrease in brain-derived neurotrophic factor at plasma level but not in serum concentrations in suicide behavior: a systematic review and meta-analysis. Brain Behav 2017;7:e00706.
362. Blake MJ, Trinder JA, Allen NB. Mechanisms underlying the association between insomnia, anxiety, and depression in adolescence: implications for behavioral sleep interventions. Clin Psychol Rev 2018;63:25-40.
363. Dietrich A, Ormel J, Buitelaar JK et al. Cortisol in the morning and dimensions of anxiety, depression, and aggression in children from a general population and clinic-referred cohort: an integrated analysis. The TRAILS study. Psychoneuroendocrinology 2013;38:1281-98.
364. Juruena MF, Eror F, Cleare AJ et al. The role of early life stress in HPA axis and anxiety. In: Kim Y-K (ed). Anxiety disorders: rethinking and understanding new discoveries. New York: Springer, 2020:141-53.
365. Vreeburg SA, Hoogendijk WJ, van Pelt J et al. Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. Arch Gen Psychiatry 2009;66:617-26.
366. Furtado M, Katzman MA. Neuroinflammatory pathways in anxiety, posttraumatic stress, and obsessive compulsive disorders. Psychiatry Res 2015; 229:37-48.
367. Gerber M, Endes K, Brand S et al. In 6-to 8-year-old children, hair cortisol is associated with body mass index and somatic complaints, but not with stress, health-related quality of life, blood pressure, retinal vessel diameters, and cardiorespiratory fitness. Psychoneuroendocrinology 2017;76:1-10.
368. Powell DJ, Liossi C, Moss-Morris R et al. Unstimulated cortisol secretory activity in everyday life and its relationship with fatigue and chronic fatigue syndrome: a systematic review and subset meta-analysis. Psychoneuroendocrinology 2013:38:2405-22.
369. Zorn JV, Schür RR, Boks MP et al. Cortisol stress reactivity across psychiatric disorders: a systematic review and meta-analysis. Psychoneuroendocrinology 2017;77:25-36.
370. Pan X, Wang Z, Wu X et al. Salivary cortisol in post-traumatic stress disorder: a systematic review and meta-analysis. BMC Psychiatry 2018;18:324.
371. Monteleone AM, Treasure J, Kan C et al. Reactivity to interpersonal stress in patients with eating disorders: a systematic review and meta-analysis of studies using an experimental paradigm. Neurosci Biobehav Rev 2018;87:133-50.
372. Naish KR, Laliberte M, MacKillop J et al. Systematic review of the effects of acute stress in binge eating disorder. Eur J Neurosci 2019;50:2415-29.
373. Goldsmith DR, Rapaport MH, Miller BJ. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. Mol Psychiatry 2016;21:1696-709.
374. Haapakoski R, Mathieu J, Ebmeier KP et al. Cumulative meta-analysis of interleukins 6 and 1β, tumour necrosis factor α and C-reactive protein in patients with major depressive disorder. Brain Behav Immun 2015;49:206-15.
375. Köhler CA, Freitas TH, Maes M et al. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. Acta Psychiatr Scand 2017;155:373-87.
376. Osimo EF, Baxter LJ, Lewis G et al. Prevalence of low-grade inflammation in depression: a systematic review and meta-analysis of CRP levels. Psychol Med 2019;49:1958-70.
377. Passos IC, Vasconcelos-Moreno MP, Costa LG et al. Inflammatory markers in post-traumatic stress disorder: a systematic review, meta-analysis, and meta-regression. Lancet Psychiatry 2015;2:1002-12.
378. Renna ME, O'Toole MS, Spaeth PE et al. The association between anxiety, traumatic stress, and obsessive-compulsive disorders and chronic inflammation: a systematic review and meta-analysis. Depress Anxiety 2018;35:1081-94.
379. Dalton B, Bartholdy S, Robinson L et al. A meta-analysis of cytokine concentrations in eating disorders. J Psychiatr Res 2018;103:252-64.
380. Jokela M, Virtanen M, Batty GD et al. Inflammation and specific symptoms of depression. JAMA Psychiatry 2016;73:87-8.
381. Miller AH. Beyond depression: the expanding role of inflammation in psychiatric disorders. World Psychiatry 2020;19:108.
382. Cryan JF, O'Riordan KJ, Cowan CS et al. The microbiota-gut-brain axis. Physiol Rev 2019;99:1877-2013.
383. Van Ameringen M, Turna J, Patterson B et al. The gut microbiome in psychiatry: a primer for clinicians. Depress Anxiety 2019;36:1004-25.
384. Jiang H, Ling Z, Zhang Y et al. Altered fecal microbiota composition in patients with major depressive disorder. Brain Behav Immun 2015;48:186-94.
385. Evans SJ, Bassis CM, Hein R et al. The gut microbiome composition associates with bipolar disorder and illness severity. J Psychiatr Res 2017;87:23-9.
386. Jiang H-Y, Zhang X, Z-H Yu et al. Altered gut microbiota profile in patients with generalized anxiety disorder. J Psychiatr Res 2018;104:130-6.
387. Pittayanon R, Lau JT, Yuan Y et al. Gut microbiota in patients with irritable bowel syndrome – a systematic review. Gastroenterology 2019;157:97-108.
388. Pinto JV, Moulin TC, Amaral OB. On the transdiagnostic nature of peripheral biomarkers in major psychiatric disorders: a systematic review. Neurosci Biobehav Rev 2017;83:97-108.
389. Clark LA. Temperament as a unifying basis for personality and psychopathology. J Abnorm Psychol 2005;114:505-21.
390. Mervielde I, De Clercq B, De Fruyt F et al. Temperament, personality, and developmental psychopathology as childhood antecedents of personality disorders. J Pers Disord 2005;19:171-201.
391. Tackett JL, Balsis S, Oltmanns TF et al. A unifying perspective on personality pathology across the life span: developmental considerations for the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders. Dev Psychopathol 2009;21:687-713.
392. Widiger TA, De Clercq B, De Fruyt F. Childhood antecedents of personality disorder: an alternative perspective. Dev Psychopathol 2009;21:771-91.
393. Letcher P, Smart D, Sanson A et al. Psychosocial precursors and correlates of differing internalizing trajectories from 3 to 15 years. Soc Dev 2009;18:618-46.
394. Brown M, Hochman A, Micali N. Emotional instability as a trait risk factor for eating disorder behaviors in adolescents: sex differences in a large-scale prospective study. Psychol Med 2019;50:1783-94.
395. Lilenfeld LR, Wonderlich S, Riso LP et al. Eating disorders and personality: a methodological and empirical review. Clin Psychol Rev 2006;26;299-320.
396. Steiner H, Kwan W, Shaffer TG et al. Risk and protective factors for juvenile eating disorders. Eur Child Adolesc Psychiatry 2003;12:i38-46.
397. Leve LD, Kim HK, Pears KC. Childhood temperament and family environment as predictors of internalizing and externalizing trajectories from ages 5 to 17. J Abnorm Child Psychol 2005;33:505-20.
398. Martel MM, Smith TE, Lee CA. Personality development and externalizing psychopathology. In: McAdams DP, Shiner RL, Tackett JL (eds). Handbook of personality development. New York: Guilford, 2019:534-50.
399. Morizot J. The contribution of temperament and personality traits to criminal and antisocial behavior development and desistance. In: Morizot J, Kazemian L (eds). The development of criminal and antisocial behavior: theory, research, and practical applications. Cham: Springer, 2015:137-65.
400. Oldehinkel AJ, Hartman CA, De Winter AF et al. Temperament profiles associated with internalizing and externalizing problems in preadolescence. Dev Psychopathol 2004;16:421-40.
401. Rhee SH, Lahey BB, Waldman ID. Comorbidity among dimensions of childhood psychopathology: converging evidence from behavior genetics. Child Dev Perspect 2015;9:26-31.
402. Smart D, Hayes A, Sanson A et al. Mental health and wellbeing of Australian adolescents: pathways to vulnerability and resilience. Int J Adolesc Med Health 2007;19:263-8.
403. Forbes MK, Rapee RM, Camberis AL et al. Unique associations between childhood temperament characteristics and subsequent psychopathology symptom trajectories from childhood to early adolescence. J Abnorm Child Psychol 2017;45:1221-33.
404. Dodd HF, Hudson JL, Rapee RM. Temperament in youth internalizing disorders. In: McKay D, Abramowitz JS, Storch EA (eds). Treatments for psychological problems and syndromes. Hoboken: Wiley, 2017:504-24.

405. Vreeke LJ, Muris P. Relations between behavioral inhibition, Big Five personality factors, and anxiety disorder symptoms in non-clinical and clinically anxious children. Child Psychiatry Hum Dev 2012;43:884-94.
406. Nielsen IKM. The impact of temperamental dimensions on change in symptoms of oppositional defiant disorder from preschool to first grade. Master's Thesis, Norwegian University of Science and Technology, Trondheim, 2014.
407. Le Grange D, O'Connor M, Hughes EK et al. Developmental antecedents of abnormal eating attitudes and behaviors in adolescence. Int J Eat Disord 2014;47:813-24.
408. Martin GC, Wertheim EH, Prior M et al. A longitudinal study of the role of childhood temperament in the later development of eating concerns. Int J Eat Disord 2000;27:150-62.
409. Beesdo K, Bittner A, Pine DS et al. Incidence of social anxiety disorder and the consistent risk for secondary depression in the first three decades of life. Arch Gen Psychiatry 2007;64:903-12.
410. Bruce SE, Yonkers KA, Otto MW et al. Influence of psychiatric comorbidity on recovery and recurrence in generalized anxiety disorder, social phobia and panic disorder: a 12-year prospective study. Am J Psychiatry 2005;162:1179-87.
411. Ruscio AM, Hallion LS, Lim CC et al. Cross-sectional comparison of the epidemiology of DSM-5 generalized anxiety disorder across the globe. JAMA Psychiatry 2017;74:465-75.
412. Jacobi F, Wittchen H-U, Hölting C et al. Prevalence, co-morbidity and correlates of mental disorders in the general population: results from the German National Health Interview and Examination Survey (GHS). Psychol Med 2004;34:597-611.
413. Narrow WE, Rae DS, Robins LN et al. Revised prevalence estimates of mental disorders in the United States. Arch Gen Psychiatry 2002;59:115-23.
414. Johnson JG, Cohen P, Kasen S et al. Cumulative prevalence of personality disorders between adolescence and adulthood. Acta Psychiatr Scand 2008; 118:410-3.
415. Wade TD, Keski-Rahkonen A, Hudson JI. Epidemiology of eating disorders. In: Tsuang MT, Tohen M, Jones PB (eds). Textbook of psychiatric epidemiology, 3rd ed. New York: Wiley, 2011:343-60.
416. Lahey BB, Zald DH, Hakes JK et al. Patterns of heterotypic continuity associated with the cross-sectional correlational structure of prevalent mental disorders in adults. JAMA Psychiatry 2014;71:989-96.
417. Shea MT, Yen S. Stability as a distinction between Axis I and Axis II disorders. J Pers Disord 2003;17:373-86.
418. Eaton WW, Shao H, Nestadt G et al. Population-based study of first onset and chronicity in major depressive disorder. Arch Gen Psychiatry 2008;65:513-20.
419. Gunderson JG, Stout RL, McGlashan TH et al. Ten-year course of borderline personality disorder: psychopathology and function from the Collaborative Longitudinal Personality Disorders study. Arch Gen Psychiatry 2011;68:827-37.
420. Zanarini MC, Frankenburg FR, Reich DB et al. Attainment and stability of sustained symptomatic transmission and recovery among patients with borderline personality disorder and axis II comparison subjects: a 16-year prospective follow-up study. Am J Psychiatry 2012;169:476-83.
421. Keel PK, Brown TA. Update on course and outcome in eating disorders. Int J Eat Disord 2010;43:195-204.
422. Caspi A, Houts RM, Ambler A et al. Longitudinal assessment of mental health disorders and comorbidities across 4 decades among participants in the Dunedin Birth Cohort Study. JAMA Netw Open 2020;3:e203221.
423. Allegrini AG, Cheesman R, Rimfeld K et al. The p factor: genetic analyses support a general dimension of psychopathology in childhood and adolescence. J Child Psychol Psychiatry 2020;61:30-9.
424. Forbes MK, Tackett JL, Markon KE et al. Beyond comorbidity: toward a dimensional and hierarchical approach to understanding psychopathology across the life span. Dev Psychopathol 2016;28:971-86.
425. Moffitt TE, Harrington HL, Caspi A et al. Depression and generalized anxiety disorder: cumulative and sequential comorbidity in a birth cohort followed to age 32. Arch Gen Psychiatry 2007;64:651-60.
426. Lieb R, Zimmerman P, Friis RH et al. The natural course of DSM-IV somatoform disorders and syndromes among adolescents and young adults: a prospective-longitudinal community study. Eur Psychiatry 2002;17:321-31.
427. Fergusson DM, Horwood LJ, Boden JM. Structure of internalising symptoms in early adulthood. Br J Psychiatry 2006;189:540-6.
428. Gustavson D, Franz C, Panizzon M et al. Internalizing and externalizing psychopathology in middle age: genetic and environmental architecture and stability of symptoms over 15 to 20 years. Psychol Med 2020;50:1530-8.
429. Waszczuk MA, Zavos HM, Gregory AM et al. The stability and change of etiological influences on depression, anxiety symptoms and their co-occurrence across adolescence and young adulthood. Psychol Med 2016;46:161-75.
430. Wertz J, Zavos H, Matthews T et al. Why some children with externalizing problems develop internalizing problems: testing two pathways in a genetically sensitive cohort study. J Child Psychol Psychiatry 2015;56:738-46.
431. Wright AG, Beltz AM, Gates KM et al. Examining the dynamic structure of daily internalizing and externalizing behavior at multiple levels of analysis. Front Psychol 2015;6:1914.
432. Butler AC, Chapman JE, Forman EM et al. The empirical status of cognitive-behavioral therapy: a review of meta-analyses. Clin Psychol Rev 2006;26:17-31.
433. Hofmann SG, Asnaani A, Vonk IJ et al. The efficacy of cognitive behavioral therapy: a review of meta-analyses. Cogn Ther Res 2012;36:427-40.
434. Newby JM, McKinnon A, Kuyken W et al. Systematic review and meta-analysis of transdiagnostic psychological treatments for anxiety and depressive disorders in adulthood. Clin Psychol Rev 2015;40:91-110.
435. García-Escalera J, Chorot P, Valiente RM et al. Efficacy of transdiagnostic cognitive-behavioral therapy for anxiety and depression in adults, children and adolescents: a meta-analysis. Rev de Psicopatol y Psicol Clin 2016;21:147-75.
436. Sun M, Rith-Najarian LR, Williamson TJ et al. Treatment features associated with youth cognitive behavioral therapy follow-up effects for internalizing disorders: a meta-analysis. J Clin Child Adolesc Psychol 2019;48(Suppl. 1):S269-83.
437. Norton PJ. An open trial of a transdiagnostic cognitive-behavioral group therapy for anxiety disorder. Behav Ther 2008;39:242-50.
438. Barlow DH, Farchione TJ, Sauer-Zavala S et al. Unified protocol for transdiagnostic treatment of emotional disorders: Therapist guide. New York: Oxford University Press, 2017.
439. Barlow DH, Harris BA, Eustis EH et al. The unified protocol for transdiagnostic treatment of emotional disorders. World Psychiatry 2020;19:245-6.
440. Steele SJ, Farchione TJ, Cassiello-Robbins C et al. Efficacy of the Unified Protocol for transdiagnostic treatment of comorbid psychopathology accompanying emotional disorders compared to treatments targeting single disorders. J Psychiatr Res 2018;104:211-6.
441. de Ornelas Maia AC, Braga A, Azevedo A et al. Transdiagnostic treatment using a unified protocol: application for patients with a range of comorbid mood and anxiety disorders. Trends Psychiatry Psychother 2013;35:134-40.
442. de Ornelas Maia AC, Sanford J, Boettcher H et al. Improvement in quality of life and sexual functioning in a comorbid sample after the unified protocol transdiagnostic group treatment. J Psychiatr Res 2017; 93:30-6.
443. Farchione TJ, Fairholme CP, Ellard KK et al. Unified protocol for transdiagnostic treatment of emotional disorders: a randomized controlled trial. Behav Ther 2012;43:666-78.
444. Sauer-Zavala S, Bentley KH, Steele SJ et al. Treating depressive disorders with the Unified Protocol: a preliminary randomized evaluation. J Affect Disord 2020;264:438-45.
445. Bullis JR, Fortune MR, Farchione TJ et al. A preliminary investigation of the long-term outcome of the Unified Protocol for Transdiagnostic Treatment of Emotional Disorders. Compr Psychiatry 2014;55:1920-7.
446. Black M, Hitchcock C, Bevan AO et al. The HARMONIC trial: study protocol for a randomised controlled feasibility trial of Shaping Healthy Minds – a modular transdiagnostic intervention for mood, stressor-related and anxiety disorders in adults. BMJ Open 2018;8:e024546.
447. Chorpita BF, Daleiden EL, Park AL et al. Child STEPs in California: a cluster randomized effectiveness trial comparing modular treatment with community implemented treatment for youth with anxiety, depression, conduct problems, or traumatic stress. J Consult Clin Psychol 2017;85:13-25.
448. de Mello MF, de Jesus Mari J, Bacaltchuk J et al. A systematic review of research findings on the efficacy of interpersonal therapy for depressive disorders. Eur Arch Psychiatry Clin Neurosci 2005;255:75-82.
449. Fairburn CG, Bailey-Straebler S, Basden S et al. A transdiagnostic comparison of enhanced cognitive behaviour therapy (CBT-E) and interpersonal psychotherapy in the treatment of eating disorders. Behav Res Ther 2015;70:64-71.
450. Elkin I, Shea MT, Watkins JT et al. National Institute of Mental Health Treatment Of Depression Collaborative Research Program. General effectiveness of treatments. Arch Gen Psychiatry 1989;46:971-82.
451. Frank E. Interpersonal and social rhythm therapy prevents depressive symptomatology in bipolar I patients. Bipolar Disord 1999;1(Suppl.):113.
452. Frank E, Kupfer DJ, Wagner EF et al. Efficacy of interpersonal psychotherapy as a maintenance treatment of recurrent depression: contributing factors. Arch Gen Psychiatry 1991;48:1053-9.
453. Stangier U, Schramm E, Heidenreich T et al. Cognitive therapy vs interpersonal psychotherapy in social anxiety disorder: a randomized controlled

trial. Arch Gen Psychiatry 2011;68:692-700.
454. Kroenke K. Patients presenting with somatic complaints: epidemiology, psychiatric co-morbidity and management. Int J Methods Psychiatr Res 2003; 12:34-43.
455. Kleinstäuber M, Witthöft M, Hiller W. Efficacy of short-term psychotherapy for multiple medically unexplained physical symptoms: a meta-analysis. Clin Psychol Rev 2011;31:146-60.
456. Kroenke K, Swindle R. Cognitive-behavioral therapy for somatization and symptom syndromes: a critical review of controlled clinical trials. Psychother Psychosom 2000;69:205-15.
457. Olatunji BO, Kauffman BY, Meltzer S et al. Cognitive-behavioral therapy for hypochondriasis/health anxiety: a meta-analysis of treatment outcome and moderators. Behav Res Ther 2014;58:65-74.
458. van Dessel N, den Boeft M, van der Wouden JC et al. Non-pharmacological interventions for somatoform disorders and medically unexplained symptoms (MUPS) in adults. Cochrane Database Syst Rev 2014;11:CD011142.
459. Jakubovski E, Johnson JA, Nasir M et al. Systematic review and meta-analysis: dose-response curve of SSRIs and SNRIs in anxiety disorders. Depress Anxiety 2019;36:198-212.
460. Locher C, Koechlin H, Zion SR et al. Efficacy and safety of selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and placebo for common psychiatric disorders among children and adolescents: a systematic review and meta-analysis. JAMA Psychiatry 2017;74:1011-20.
461. Cipriani A, Barbui C, Salanti G et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. Lancet 2011;378:1306-15.
462. Pae CU, Lim HK, Peindl K et al. The atypical antipsychotics olanzapine and risperidone in the treatment of posttraumatic stress disorder: a meta-analysis of randomized, double-blind, placebo-controlled clinical trials. Int Clin Psychopharmacol 2008;23:1-8.
463. Perlis RH, Welge JA, Vornik LA et al. Atypical antipsychotics in the treatment of mania: a meta-analysis of randomized, placebo-controlled trials. J Clin Psychiatry 2006;67:509-16.
464. Zhou X, Keitner GI, Qin B et al. Atypical antipsychotic augmentation for treatment-resistant depression: a systematic review and network meta-analysis. Int J Neuropsychopharmacol 2015;18:pyv060.
465. Maher AR, Maglione M, Bagley S et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults. JAMA 2011;306:1359-69.
466. Attia E, Steinglass JE, Walsh BT et al. Olanzapine versus placebo in adult outpatients with anorexia nervosa: a randomized clinical trial. Am J Psychiatry 2019;176:449-56.
467. Spielmans GI, Berman MI, Linardatos E et al. Adjunctive atypical antipsychotic treatment for major depressive disorder: a meta-analysis of depression, quality of life, and safety outcomes. PLoS Med 2013;10:e1001403.
468. Kleinstäuber M, Witthöft M, Steffanowski A et al. Pharmacological interventions for somatoform disorders in adults. Cochrane Database Syst Rev 2014;11:CD010628.
469. Reed GM, Sharan P, Rebello TJ et al. The ICD-11 developmental field study of reliability of diagnoses of high-burden mental disorders: results among adult patients in mental health settings of 13 countries. World Psychiatry 2018;17:174-86.
470. Eaton NR, Krueger RF, Oltmanns TF. Aging and the structure and long-term stability of the internalizing spectrum of personality and psychopathology. Psychol Aging 2011;26:987-93.
471. Waszczuk MA, Kotov R, Ruggero C et al. Hierarchical structure of emotional disorders: from individual symptoms to the spectrum. J Abnorm Psychol 2017;126:613-34.
472. Waszczuk MA, Zimmerman M, Ruggero C et al. What do clinicians treat: diagnoses or symptoms? The incremental validity of a symptom-based, dimensional characterization of emotional disorders in predicting medication prescription patterns. Compr Psychiatry 2017;79:80-8.
473. Forbush KT, Chen PY, Hagan KE et al. A new approach to eating-disorder classification: using empirical methods to delineate diagnostic dimensions and inform care. Int J Eat Disord 2018;51:710-21.
474. Dalgleish T, Black M, Johnson D et al. Transdiagnostic approaches to mental health problems: current status and current directions. J Consult Clin Psychol 2020;88:179-95.
475. Keeley JW, Reed GM, Roberts MC et al. Developing a science of clinical utility in diagnostic classification systems: field study strategies for ICD-11 mental and behavioral disorders. Am Psychol 2016;71:3-16.
476. Glover NG, Crego C, Widiger TA. The clinical utility of the Five Factor Model of personality disorder. Personal Disord 2012;3:176-84.
477. Lowe JR, Widiger TA. Clinicians' judgments of clinical utility: a comparison of the DSM-IV with dimensional models of general personality. J Pers Disord 2009;23:211-29.
478. Morey LC, Skodol AE, Oldham JM. Clinician judgments of clinical utility: a comparison of DSM-IV-TR personality disorders and the alternative model for DSM-5 personality disorders. J Abnorm Psychol 2014;123:398-405.
479. Samuel DB, Widiger TA. Clinicians' use of personality disorder models within a particular treatment setting: a longitudinal comparison of temporal consistency and clinical utility. Personal Ment Health 2011;5:12-28.
480. Moscicki EK, Clarke DE, Kuramoto SJ et al. Testing DSM-5 in routine clinical practice settings: feasibility and clinical utility. Psychiatr Serv 2013;64:952-60.
481. Ruggero CJ, Kotov R, Hopwood CJ al. Integrating the Hierarchical Taxonomy of Psychopathology (HiTOP) into clinical practice. J Consult Clin Psychol 2019;87:1069-84.
482. Nichols JH, Christenson RH, Clarke W et al. Executive summary. The National Academy of Clinical Biochemistry Laboratory Medicine Practice Guideline: evidence-based practice for point-of-care testing. Clin Chim Acta 2007;379:14-28.
483. Whelton PK, Carey RM, Aronow WS et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2018;71:e127-248.
484. Hamilton MA. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56-62.
485. Beck AT, Steer RA, Brown GK. Manual for the Beck Depression Inventory II. San Antonio: Psychological Corporation, 1996.
486. Beck AT, Epstein N, Brown G et al. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 1988;56:893-7.
487. Kroenke K, Spitzer RL, Williams JB et al. The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: a systematic review. Gen Hosp Psychiatry 2010;32:345-59.
488. Posner K, Brown GK, Stanley B et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 2011;168:1266-77.
489. Watson D, O'Hara MW, Simms LJ et al. Development and validation of the Inventory of Depression and Anxiety Symptoms (IDAS). Psychol Assess 2007;19:253-68.
490. Dornbach-Bender A, Ruggero CJ, Waszczuk MA et al. Mapping emotional disorders at the finest level: convergent validity and joint structure based on alternative measures. Compr Psychiatry 2017;79:31-9.
491. Forbush KT, Bohrer BK, Hagan KE et al. Development and initial validation of the Eating Pathology Symptoms Inventory-Clinician Rated Version (EPSI-CRV). Psychol Assess 2020;32:943-55.
492. Forbes MK, Baillie AJ, Schniering CA. Critical flaws in the Female Sexual Function Index and the International Index of Erectile Function. J Sex Res 2014;51:485-91.
493. Kotov R, Gamez W, Schmidt F et al. Linking "Big" personality traits to anxiety, depressive, and substance use disorders: a meta-analysis. Psychol Bull 2010;136:768-821.
494. Krueger RF, Derringer J, Markon KE et al. Initial construction of a maladaptive personality trait model and inventory for DSM-5. Psychol Med 2012;42:1879-90.
495. Calabrese WR, Rudick MM, Simms LJ et al. Development and validation of Big Four personality scales for the schedule for nonadaptive and adaptive personality-second edition (SNAP-2). Psychol Assess 2012;24:751-63.
496. Livesley WJ, Jackson DN. Manual for the Dimensional Assessment of Personality Pathology - Basic Questionnaire. Port Huron: Sigma Press, 2009.
497. Sellbom M, Solomon-Krakus S, Bach B et al. Validation of Personality Inventory for DSM-5 (PID-5) algorithms to assess ICD-11 personality trait domains in a psychiatric sample. Psychol Assess 2020;32:40-9.
498. Wright AG, Thomas KM, Hopwood CJ et al. The hierarchical structure of DSM-5 pathological personality traits. J Abnorm Psychol 2012;121:951-7.
499. Ben-Porath YS, Tellegen A. Minnesota Multiphasic Personality Inventory-2-Restructured Form. Bloomington: Pearson Assessments, 2008.
500. Morey LC. Professional manual for the Personality Assessment Inventory, 2nd ed. Lutz: Psychological Assessment Resources, 2007.
501. Lee TT, Sellbom M, Hopwood CJ. Contemporary psychopathology assessment: mapping major personality inventories onto empirical models of psychopathology. In: Bowden SC (ed). Neuropsychological assessment in the age of evidence-based practice: diagnostic and treatment evaluations. New

York: Oxford University Press, 2017:65-94.
502. Sellbom M. The MMPI-2-Restructured Form (MMPI-2-RF): assessment of personality and psychopathology in the twenty-first century. Annu Rev Clin Psychol 2019;15:149-77.
503. Zijlema WL, Stolk RP, Löwe B et al. How to assess common somatic symptoms in large-scale studies: a systematic review of questionnaires. J Psychosom Res 2013;74:459-68.
504. Kroenke K, Spitzer RL, Degruy FV et al. A symptom checklist to screen for somatoform disorders in primary care. Psychosomatics 1998;39:263-72.
505. Derogatis LR, Lipman RS, Covi L. SCL-90: an outpatient psychiatric rating scale – preliminary report. Psychopharmacol Bull 1973;9:13-28.
506. Pilowsky I. Dimensions of hypochondriasis. Br J Psychiatry 1967;113:89-93.
507. Kessler RC, DuPont RL, Berglund P et al. Impairment in pure and comorbid generalized anxiety disorder and major depression at 12 months in two national surveys. Am J Psychiatry 1999;156:1915-23.
508. Kessler RC, McGonagle KA, Zhao S et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8-19.
509. Kessler RC, Mickelson KD, Zhao S. Patterns and correlates of self-help group membership in the United States. Soc Policy 1997;27:27-46.
510. Magee WJ, Eaton WW, Wittchen H-U et al. Agoraphobia, simple phobia, and social phobia in the National Comorbidity Survey. Arch Gen Psychiatry 1996;53:159-68.
511. Plana-Ripoll O, Musliner KL, Dalsgaard S et al. Nature and prevalence of combinations of mental disorders and their association with excess mortality in a population-based cohort study. World Psychiatry 2020;19:339-49.
512. Ellard KK, Fairholme CP, Boisseau CL et al. Unified protocol for the transdiagnostic treatment of emotional disorders: protocol development and initial outcome data. Cogn Behav Pract 2010;17:88-101.
513. Barlow DH, Sauer-Zavala S, Carl JR et al. The nature, diagnosis and treatment of neuroticism: back to the future. Clin Psychol Sci 2014;2:344-65.
514. Sauer-Zavala S, Wilner JG, Barlow DH. Addressing neuroticism in psychological treatment. Personal Disord 2017;8:228-36.
515. Stasik-O'Brien SM, Brock RL, Chmielewski M et al. Clinical utility of the Inventory of Depression and Anxiety Symptoms (IDAS). Assessment 2019; 26:944-60.
516. Lengel CJ, Helle AC, DeShong HL et al. Translational applications of personality science for the conceptualization and treatment of psychopathology. Clin Psychol Sci Pract 2016;23:288-308.
517. Kotov R, Krueger RF, Watson D et al. The Hierarchical Taxonomy of Psychopathology (HiTOP): a quantitative nosology based on consensus of evidence. Annu Rev Clin Psychol 2021;17:83-108.
518. Alloy L, Kelly M, Mineka S et al. Comorbidity in anxiety and depressive disorders: a helplessness/ hopelessness perspective. In: Maser JD, Cloninger CR (eds). Comorbidity of mood and anxiety disorders. Washington: American Psychiatric Press, 1990:499-543.
519. Jacobson NC, Newman MG. Anxiety and depression as bidirectional risk factors for one another: a meta-analysis of longitudinal studies. Psychol Bull 2017;143:1155-200.

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